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(21) International Application Number: PCT/US95/12365 (22) International Filing Date: 10 October 1995 (10.10.95) (30) Priority Data: 08/321,183 11 October 1994 (11.10.94) US (60) Parent Application or Grant (63) Related by Continuation US 08/321,183 (CON) Filed on 11 October 1994 (11.10.94) (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): CHANDRAKUMAR, Nizal, Samuel [IN/US]; 15 Montgomery Lane, Vernon Hills, IL 60061 (US). CHEN, Barbara, Baosheng [US/US]; 1921 Robincrest Lane, Glenview, IL 60025 (US). CLARE, Michael [GB/US]; 5154 W. Brown, Skokie, IL 60077 (US). DESAI, Bipinchandra, Nanubhai [IN/US]; 200 Annapolis		Drive, Vernon Hills, IL 60061 (US). DJURIC, Steven, Wakefield [GB/US]; 924 Dolphin Drive, Malvern, PA 19355 (US). DOCTER, Stephan, Hermann [US/US]; 320 Marcella Road, Mount Prospect, IL 60056 (US). GASIECKI, Alan, Frank [US/US]; 105 Alexandria Drive, Vernon Hills, IL 60061 (US). HAACK, Richard, Arthur [US/US]; 5356 North Luna, Chicago, IL 60630 (US). LIANG, Chi-Dean [US/US]; 1416 Evergreen Terrace, Glenview, IL 60025 (US). MIYASHIRO, Julie, Marion [US/US]; 1260 West Columbia, Chicago, IL 60626 (US). PENNING, Thomas, Dale [US/US]; 374 Larch Avenue, Elmhurst, IL 60126 (US). RUSSELL, Mark, Andrew [GB/US]; 475 Cross Road, Gurnee, IL 60031 (US). YU, Stella, Siu-tzyy [US/US]; 7801 Maple Street, Morton Grove, IL 60053 (US). (74) Agents: FEDER, Scott, B. et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: LTA ₄ HYDROLASE INHIBITORS (57) Abstract <p>The present invention provides compounds of the formula Ar¹-Q-Ar²-Y-R-Z and pharmaceutically acceptable salts thereof wherein Ar¹ and Ar² are optionally substituted aryl moieties, Z is an optionally substituted nitrogen-containing moiety which may be an acyclic, cyclic or bicyclic amine or an optionally substituted monocyclic or bicyclic nitrogen-containing heteroaromatic moiety; Q is a linking group capable of linking two aryl groups; R is an alkylene moiety; Y is a linking moiety capable of linking an aryl group to an alkylene moiety and wherein Z is bonded to R through a nitrogen atom. The compounds and pharmaceutical compositions of the present invention are useful in the treatment of inflammatory diseases which are mediated by LTB₄ production, such as psoriasis, ulcerative colitis, IBD and asthma.</p>		

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LTA₄ HYDROLASE INHIBITORSFIELD OF THE INVENTION

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This invention relates generally to anti-inflammatory compounds and pharmaceutical compositions, and more particularly to anti-inflammatory compounds and compositions which are capable of inhibiting leukotriene A₄ hydrolase.

LTA₄ hydrolase is a requisite enzyme in the biosynthetic pathway leading to LTB₄ formation. LTB₄ is a proinflammatory compound. R. Lewis, et al., *N. Engl. J. Med.* 323, 645-655 (1990) have demonstrated that LTB₄ is a potent granulocyte agonist inducing chemotaxis, aggregation, degranulation, adherence and priming of inflammatory cells for induction by other agonists. Binding of LTB₄ to receptors is stereospecific with two distinct classes of binding sites. A. Lin, et al., *Prostaglandins* 28, 837-849 (1984). A high affinity site [$4-5 \times 10^{-10}$ M] mediates chemotaxis and chemokinesis while lower affinity sites [$0.6-5 \times 10^{-7}$ M] stimulate granular secretion and oxidative burst. The LTB₄ receptor is associated with a GTP-binding protein that regulates affinity and transduces signals. T. Schepers, et al., *J. Biol. Chem.* 267, 159-165 (1992). Elevated LTB₄ levels have been reported for many diseases. Most prominently, elevated LTB₄ levels have been correlated to the pathology of inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis and in psoriasis. P. Sharon, et al., *Gastroent.* 86, 453-460; K. Lauritsen, et al., *Gastroent.* 95, 11-17 (1989); S. Brain, et al., *Br. J. Pharm.*, 83, 313-317 (1984). Other properties of LTB₄ which may contribute to disease processes are: stimulation of mucus secretion; stimulation of cytokine production; and the ability to act synergistically with other inflammatory mediators

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such as prostaglandins and cysteinyl leukotrienes thereby amplifying the inflammatory process.

B. Samuelsson, et al., *J. Biol Chem.*, 264, 19469-19472 (1989) have shown that LTB₄ biosynthesis from arachidonic acid involves the action of 2 enzymes, 5-lipoxygenase [5-LO] and LTA₄ hydrolase. 5-LO transforms arachidonic acid to 5-HPETE and subsequent formation of LTA₄, which is an unstable allylic epoxide intermediate which is enzymatically hydrolyzed by LTA₄ hydrolase to form the dihydroxy acid LTB₄.

LTA₄ hydrolase is distinct from cytosolic and microsomal epoxide hydrolases based on strict substrate requirements, product formation [5(S),12(R) vs. 5(S),6(R) for mouse liver cytosolic epoxide hydrolase, and lack of inhibition by inhibitors of cytosolic epoxide hydrolase. LTA₄ hydrolase appears to be ubiquitously distributed in mammalian tissues even in cell types that do not express 5-LO, suggesting the importance of transcellular metabolism of LTA₄. While peptidomimetic compounds such as bestatin and captopril have been shown to exhibit LTA₄ hydrolase inhibitory activity, they are not able to satisfy the requirement of a small organic compound which is capable of cellular penetration. It would therefore be very advantageous to be able to provide low molecular weight inhibitors of LTB₄ biosynthesis which preferably exhibit oral activity in vivo at desirably low concentrations.

Summary of the Invention

Applicants have now discovered that compounds of the formula I



(I)

and pharmaceutically acceptable salts and stereoisomers thereof possess LTA₄ hydrolase inhibitor activity, wherein:

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Ar¹ is an aryl moiety selected from the group consisting of:

(i) phenyl, mono-, di-, or tri-substituted phenyl with the substituents selected from the group consisting of Cl, Br, F, CF₃, lower alkyl, lower alkoxy, NH₂, NO₂ and OH;

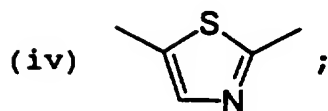
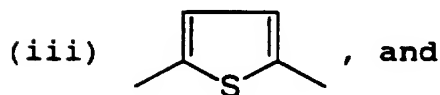
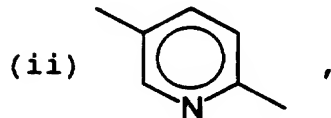
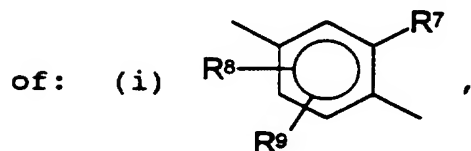
(ii) 2-, 4- or 5- thiazolyl,

(iii) 2-, 3- or 4-pyridinyl,

(iv) 2- or 3-thienyl, and

(v) 2- or 3-furyl;

Ar² is an aryl moiety selected from the group consisting



Q is selected from the group consisting of:

(i) -O-,

(ii) -CH₂-,

(iii) -OCH₂-,

(iv) -CH₂O-,

(v) -NH-;

- (vi) $\text{-NHCH}_2\text{-}$,
(vii) $\text{-CH}_2\text{NH-}$,
(viii) $\text{-CF}_2\text{-}$,
(ix) -CH=CH- ,
5 (x) $\text{-CH}_2\text{CH}_2\text{-}$, and
(xi) carbon-carbon single bond;

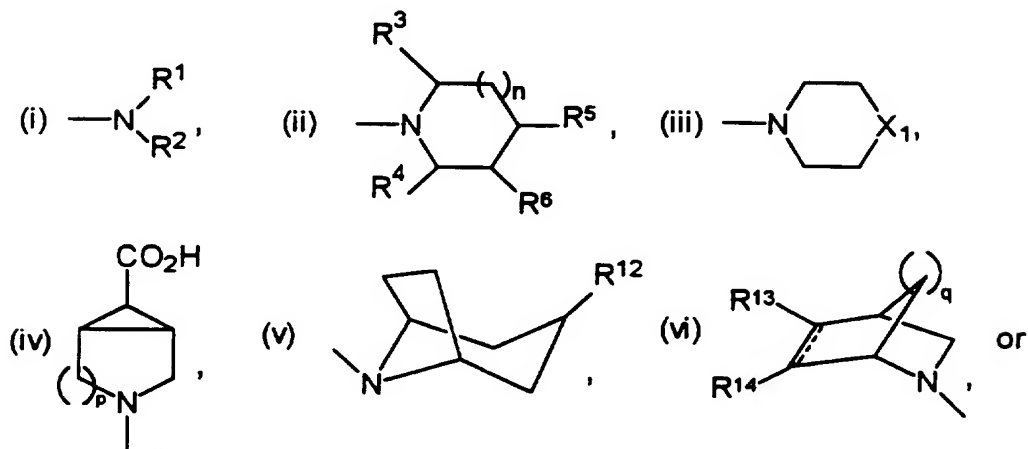
Y is selected from the group consisting of

- 10 (i)-O-,
 (ii) -S-,
 (iii) -NH-,
 (iv) -S(O)-, and
 (v) -S(O₂)-;

15 R is selected from the group consisting of:

- (i) linear or branched C₂-C₆ alkylene; or
(ii) C(R¹⁰)(R¹¹)-(CH₂)_m; and

Z is selected from the group consisting of:



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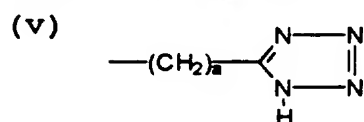
- (vii) a monocyclic or bicyclic heteroaromatic moiety having at least one heteroatom, wherein the heteroatom is nitrogen, and wherein the monocyclic heteroaromatic moiety comprises a 5- or 6-membered ring and the

- 5 -

bicyclic heteroaromatic moiety comprises a fused 9- or 10-membered ring;

wherein R^1 and R^2 are independently selected from the group consisting of:

- (i) H,
- (ii) lower alkyl or allyl,
- (iii) benzyl,
- (iv) $-(CH_2)_aCOR^{15}$,

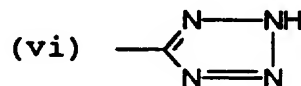


- (vi) $-(CH_2)_a-OH$

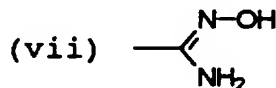
R^3 and R^4 are independently H or lower alkyl;

R^5 and R^6 are independently selected from the group consisting of:

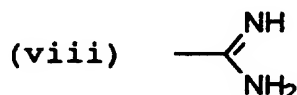
- (i) H,



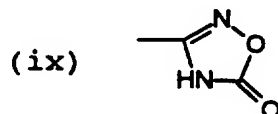
- (ii) $-OH$ or $=O$,



- (iii) $-(CH_2)_aCOR^{15}$,



- (iv) $-(CH_2)_aCONH(CH_2)_bCO_2R^{16}$,



- (v) $-NHR^{17}$,

R^7 is H, halogen, lower alkyl, lower alkoxy, nitro, hydroxy, or R^7 taken together with R^{10} is an alkylene group having one or two carbon atoms;

R^8 and R^9 are independently H, halogen, lower alkyl, lower alkoxy, NH_2 , NO_2 or OH ;

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R^{10} is H, lower alkyl, or R^{10} taken together with R^7 is an alkylene group having one or two carbon atoms;

R^{11} is H or lower alkyl;

5

R^{12} is selected from the group consisting of:

- (i) H,
- (ii) -OH or =O,
- (iii) $-(CH_2)_aCOR^{15}$,
- 10 (iv) $-(CH_2)_aCONH(CH_2)_bCO_2R^{16}$,
- (v) $-NHR^{17}$;

R^{13} and R^{14} are independently hydrogen, $-(CH_2)_aCOR^{15}$, provided that at least one of R^{13} and R^{14} is hydrogen;

15

R^{15} is $-OR^{16}$, $-NHR^{16}$ or $-NHNH_2$;

R^{16} is H, lower alkyl or benzyl;

20 R^{17} is H, lower alkyl, benzyl, $-COR^{16}$ or $-CONH_2$;

X^1 is $\begin{array}{c} \diagup \\ NR^{18} \\ \diagdown \end{array}$, -S-, or -O-, wherein R^{18} is H, lower

alkyl, $-CONH_2$, $CSNH_2$, $-COCH_3$ or $-SO_2CH_3$;

25 a and b are independently integers of from 0 to 5;

m is 1, 2 or 3;

n is 0, 1, 2 or 3;

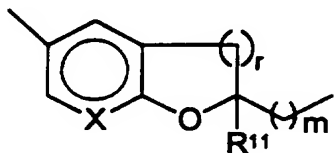
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p is 1 or 2; and

q is 1, 2 or 3;

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provided however that where R is $C(R^{10})(R^{11})-(CH_2)_m$, and R^{10} taken together with R^7 forms an alkylene group having one or two carbon atoms, then $-Ar^2-Y-R$ is



5 wherein X is $-CH-$ or $-N-$, and r is 1 or 2, further provided that wherein R^1 , R^2 or both R^1 and R^2 are $-(CH_2)_aCOR^{15}$, then a is not 0.

10 Detailed Description of the Invention

In one of its embodiments, the present invention entails compounds of the formula I



(I)

and pharmaceutically acceptable salts and stereoisomers thereof, wherein:

20 Ar^1 is an aryl moiety selected from the group consisting of:

(i) phenyl, mono-, di-, or tri-substituted phenyl with the substituents selected from the group consisting of Cl, Br, F, CF_3 , lower alkyl, lower alkoxy, NH_2 , NO_2 , and OH;

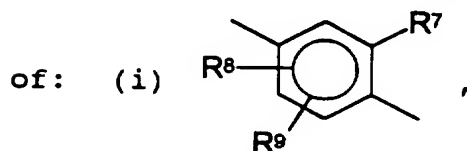
25 (ii) 2-, 4- or 5- thiazolyl,

(iii) 2-, 3- or 4-pyridinyl,

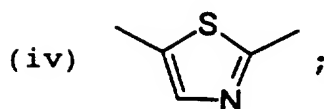
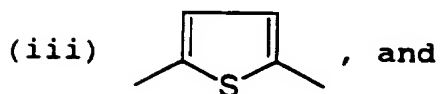
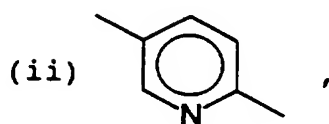
- 8 -

(iv) 2- or 3-thienyl, and

(v) 2- or 3-furyl;

 Ar^2 is an aryl moiety selected from the group consisting

5



Q is selected from the group consisting of:

10

(i) -O-,

(ii) -CH₂-,(iii) -OCH₂-,(iv) -CH₂O-,

(v) -NH-;

15

(vi) -NHCH₂-,(vii) -CH₂NH-,(viii) -CF₂-,

(ix) -CH=CH-,

(x) -CH₂CH₂-, and

20

(xi) carbon-carbon single bond;

Y is selected from the group consisting of

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- (i) -O-,
 (ii) -S-,
 (iii) -NH-,
 (iv) -S(O)-, and
 (v) -S(O₂)-;

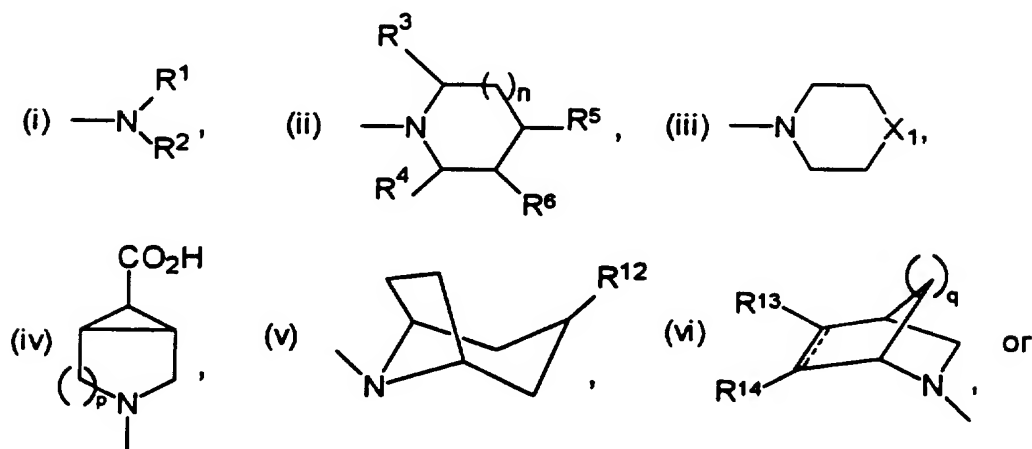
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R is selected from the group consisting of:

- (i) linear or branched C₂-C₆ alkylene; or
 (ii) C(R¹⁰)(R¹¹)-(CH₂)_m; and

10

Z is selected from the group consisting of:



- (vii) a monocyclic or bicyclic heteroaromatic moiety having at least one heteroatom, wherein the heteroatom is nitrogen, and wherein the monocyclic heteroaromatic moiety comprises a 5- or 6-membered ring and the bicyclic heteroaromatic moiety comprises a fused 9- or 10-membered ring;

15

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wherein R¹ and R² are independently selected from the group consisting of:

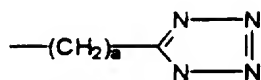
- (i) H,
 (ii) lower alkyl or allyl,
 (iii) benzyl,

25

- 10 -

(iv) $-(CH_2)_aCOR^{15}$,

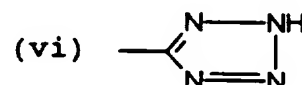
(v)

(vi) $-(CH_2)_aOH$

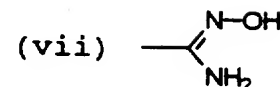
5 R^3 and R^4 are independently H or lower alkyl;

R^5 and R^6 are independently selected from the group consisting of:

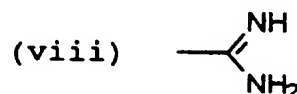
(i) H,



10

(ii) $-OH$, $=O$, or $-(CH_2)_aOH$ 

15

(iii) $-(CH_2)_aCOR^{15}$,(iv) $-(CH_2)_aCONH(CH_2)_bCO_2R^{16}$,

20

(v) $-NHR^{17}$,

R^7 is H, halogen, lower alkyl, lower alkoxy, nitro, hydroxy, or R^7 taken together with R^{10} is an alkylene group having one or two carbon atoms;

25

R^8 and R^9 are independently H, halogen, lower alkyl, lower alkoxy, NH_2 , NO_2 or OH;

R^{10} is H, lower alkyl, or R^{10} taken together with R^7 is an alkylene group having one or two carbon atoms;

30

R^{11} is H or lower alkyl;

R^{12} is selected from the group consisting of:

35

(i) H,

(ii) $-OH$ or $=O$,(iii) $-(CH_2)_aCOR^{15}$,

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(iv) $-(CH_2)_aCONH(CH_2)_bCO_2R^{16}$,(v) $-NHR^{17}$;

5 R^{13} and R^{14} are independently hydrogen, $-(CH_2)_aCOR^{15}$,
provided that at least one of R^{13} and R^{14} is hydrogen;

 R^{15} is $-OR^{16}$, $-NHR^{16}$ or $-NHNH_2$; R^{16} is H, lower alkyl or benzyl;

10

 R^{17} is H, lower alkyl, benzyl, $-COR^{16}$ or $-CONH_2$;

X^1 is $\begin{array}{c} \diagup \\ NR^{18} \\ \diagdown \end{array}$, $-S-$, or $-O-$, wherein R^{18} is H, lower

alkyl, $-CONH_2$, $CSNH_2$, $-COCH_3$ or $-SO_2CH_3$;

15

a and b are independently integers of from 0 to 5;

m is 1, 2 or 3;

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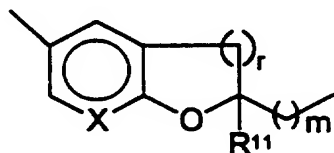
n is 0, 1, 2 or 3;

p is 1 or 2; and

q is 1, 2 or 3;

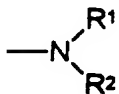
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provided however that where R is $C(R^{10})(R^{11})-(CH_2)_m$, and
 R^{10} taken together with R^7 forms an alkylene group
having one or two carbon atoms, then $-Ar^2-Y-R-$ is



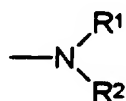
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wherein X is -CH- or -N-, and r is 1 or 2, further provided that wherein Z is

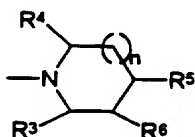


and R¹ and/or R² is -(CH₂)_aCOR¹⁵, then a is not 0.

In one of its embodiments the present invention entails compounds of formula I Ar¹-Q-Ar²-Y-R-Z, wherein Z is an amine moiety of the formula

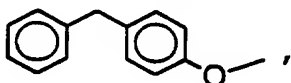


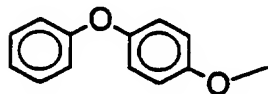
In another of its embodiments the present invention includes compounds of formula I Ar¹-Q-Ar²-Y-R-Z, wherein Z is

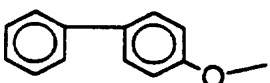


wherein R³, R⁴, R⁵ and R⁶ are defined as set forth hereinbefore.

In another of its embodiments the present invention entails compounds of the formula Ar¹-Q-Ar²-Y-

R-Z wherein when Ar¹-Q-Ar²-Y is ,



or , then (A) R¹ and R²

are not simultaneously H or lower alkyl; or (B) R³, R⁴, R⁵ and R⁶ are not simultaneously H.

The compounds of the present invention, in several embodiments, may comprise a carboxylic acid or ester moiety. It will be appreciated by the art-skilled that a compound of the present invention comprising an ester moiety is readily converted, *in vivo*, especially when

administered orally, into its corresponding carboxylic acid form. The ester-containing compounds of the present invention are therefore prodrugs of their carboxylic acid form.

5 In another of its embodiments the present invention concerns compounds of formula I $\text{Ar}^1\text{-Q-Ar}^2\text{-Y-R-Z}$, wherein Z is a monocyclic or bicyclic heteroaromatic moiety having at least one heteroatom, the at least one heteroatom being nitrogen, wherein the
10 monocyclic heteroaromatic moiety comprises a 5- or 6-membered ring and the bicyclic heteroaromatic moiety comprises a fused 9- or 10-membered ring.

In another of its aspects the invention entails pharmaceutical composition comprising a
15 pharmacologically effective amount of a compound of formula I and a pharmaceutically acceptable carrier.

In still another of its embodiments the present invention involves a method for treating a mammal exhibiting an LTB₄ mediated inflammatory condition
20 comprising administering to the mammal a pharmacologically effective amount of a compound of formula I.

The term "lower alkyl" means straight or branched chain alkyl having 1 to 6 carbon atoms such as methyl,
25 ethyl, propyl, butyl, pentyl, hexyl and the branched chain isomers thereof.

The term "lower alkoxy" means straight or branched chain alkoxy having 1 to 6 carbon atoms such as methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and
30 the branched chain isomers thereof.

The term "allyl" as used herein means the 1-propenyl radical, $-\text{CH}_2\text{-CH}=\text{CH}_2$.

The term "halo" means fluoro, cloro, bromo, or iodo.

35 The phrase "monocyclic or bicyclic heteroaromatic moiety" having at least one heteroatom which is nitrogen, includes but is not limited to imidazole,

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triazole, benzimidazole, imidazopyridine, triazolopyridine, thiazole, purine and the like. Such monocyclic and bicyclic heteroaromatic moieties having at least two nitrogen atoms may be bonded, in a compound of the present invention, through any of the nitrogen atoms, as will be appreciated by the person of ordinary skill in the art, to provide two or more conformational isomers.

Such monocyclic heteroaromatic and bicyclic heteroaromatic compounds are included in the group of compounds referred to herein as "ZH", which group also includes non-aromatic compounds. Non-aromatic compounds which are contemplated by reference to "ZH" include acyclic amines, monocyclic amines, and bicyclic amines as defined herein. A compound of formula I, which comprises a "Z moiety" may be readily formed by reacting a compound of the formula $\text{Ar}^1\text{-Q-Ar}^2\text{-R-Cl}$ or $\text{Ar}^1\text{-Q-Ar}^2\text{-R-OTs}$ with an amine or heteroaromatic compound, ZH.

Included within the classes and subclasses of compounds embraced by Formula I are isomeric forms of the described compounds including diastereoisomers, enantiomers and tautomeric forms of the described compounds. Pharmaceutically acceptable salts of such compounds are also included as well as pharmaceutically acceptable salts of such isomers and tautomers.

In the structures herein a bond drawn across a bond in a ring indicates that the bond can be to any available atom of the ring structure.

The expression "pharmaceutically acceptable salts" is intended to include those salts capable of being formed with the compounds of the present invention without materially altering the chemical structure or pharmacological properties thereof. Such salts include inorganic and organic cations or acid addition salts, such as sodium, potassium, calcium, ammonium, alkylammonium, quaternary ammonium, triethanolamine,

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lysine, hydrochloride, hydrobromide, etc. well known to those skilled in the art. The foregoing salts are prepared in the conventional manner by neutralization of the compounds of formula I with the desired base or acid.

The compounds of the present invention can be administered to a patient in such oral dosage forms as tablets, capsules, pills, powders, granules, elixirs or syrups, as well as aerosols for inhalation. Likewise, administration may be effected intravascularly, subcutaneously, or intramuscularly using dosage forms known to those of ordinary skill in the pharmaceutical arts. In general, the preferred form of administration is oral. An effective but non-toxic amount of the compound is employed in treatment. The dosage regimen utilizing the present compounds is selected in accordance with a variety of factors including the type, age, weight, sex and medical condition of the patient; the severity of the condition to be ameliorated; and the route of administration. A physician of ordinary skill can readily determine and prescribe a "pharmaceutically effective amount" of a compound of Formula I, that is, the effective amount of the compound required to prevent, treat or arrest the progress of the condition. Dosages of the compounds of the present invention will range generally between 0.1 mg/kg/day to about 100 mg/kg/day and preferably between about 0.5 mg/kg/day to about 50 mg/kg/day when administered to patients suffering from allergic or hypersensitivity reactions or inflammation. The compounds may also be administered transdermally or topically to treat proliferative skin conditions such as psoriasis. The daily dosage may be administered in a single dose or in equal divided doses three to four times daily.

As used herein the phrase "LTA₄ hydrolase inhibitor" means a compound which is capable of

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exhibiting an IC_{50} of less than 1 mM in an in vitro assay employing 10 μ g/ml of LTA_4 hydrolase enzyme (specific activity 600 nMoles LTB_4 /min/mg of enzyme) in the presence of 25 μ M substrate (LTA_4) in a total
5 reaction volume of 100 μ l.

In the pharmaceutical compositions and methods of the present invention, at least one of the active compounds of formula I or a pharmaceutically acceptable salt thereof will typically be administered in
10 admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and
15 consistent with conventional pharmaceutical practices. For instance, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch,
20 sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol and the like; for oral administration in liquid form, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as
25 ethanol and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic
30 gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Lubricants for use in these dosage forms include boric acid, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without
35 limitation, starch, methylcellulose, agar, bentonite, guar gum and the like.

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By virtue of their activity as LTA₄ hydrolase inhibitors, the compounds of Formula I are useful in treating inflammatory conditions mediated by LTB₄ production in mammals such as psoriasis, contact and atropic dermatitis, Crohn's disease, ulcerative colitis, inflammatory bowel disease, multiple sclerosis, ankylosing spondylitis arthritis, asthma and the like. Similarly, the compounds of Formula I can be used in preventing recurring inflammatory attacks. A physician or veterinarian of ordinary skill can readily determine whether a subject exhibits the inflammatory condition. A preferred utility relates to treatment of ulcerative colitis.

Among the compounds of the present invention which possess LTA₄ hydrolase inhibiting activity are the following:

1-[2-(4-phenoxyphenoxy)ethyl]pyrrolidine;
1-[2-(4-phenylmethyl)phenoxyethyl]pyrrolidine;
1-[2-[4-(2-phenylethenyl)phenoxy]ethyl]pyrrolidine;
1-[2-[4-(4-fluorophenoxy)phenoxy]ethyl]pyrrolidine;
4-[[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]methyl]thiazole;
1-[2-[4-(phenylmethoxy)phenoxy]ethyl]pyrrolidine;
4-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzoic acid;
4-[4-[2-(1-pyrrolidinyl)ethoxy]phenoxy]benzoic acid;
5-phenoxy-2-[2-(1-pyrrolidinyl)ethoxy]pyridine;
1-[2-[4-(2-phenylethyl)phenoxy]ethyl]pyrrolidine;
1-[2-[4-[(difluoro)phenylmethyl]phenoxy]ethyl]-pyrrolidine;
1-[2-[4-(phenylmethyl)phenylthio]ethyl]pyrrolidine,
monohydrochloride;
1-[2-[4-(phenylmethyl)phenylsulfinyl]ethyl]pyrrolidine,
monohydrochloride;
N-[[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]methyl]-3-pyridinamine;
N-(4-phenoxyphenyl)-1-pyrrolidine ethanamine,
monohydrochloride;
5-(phenylmethyl)-2-[2-(1-pyrrolidinyl)ethoxy]thiazole;

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- 1-[2-[2-fluoro-4-(phenylmethyl)phenoxy]ethyl]-pyrrolidine;
1-[2-[3-fluoro-4-(phenylmethyl)phenoxy]ethyl]-pyrrolidine;
5 1-[2-[2-methyl-4-(phenylmethyl)phenoxy]ethyl]-pyrrolidine;
1-[2-[2,6-difluoro-4-(phenylmethyl)phenoxy]ethyl]-pyrrolidine;
2-[4-[2-(1-pyrrolidinyl)ethoxy]phenylmethyl]thiazole;
10 5-[[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]methyl]thiazole;
methyl 5-(phenylmethyl)-2-[2-(1-pyrrolidinyl)ethoxy]-benzoate;
3-[4-[2-(1-pyrrolidinyl)ethoxy]phenylmethyl]pyridine;
4-[4-[2-(1-pyrrolidinyl)ethoxy]phenylmethyl]pyridine;
15 1-[2-[4-[(3-methoxyphenyl)methyl]phenoxy]ethyl]-pyrrolidine;
1-[2-[4-[4-(methoxyphenyl)methyl]phenoxy]ethyl]-pyrrolidine;
1-[2-[4-[(2-methoxyphenyl)methyl]phenoxy]ethyl]-pyrrolidine;
20 1-[2-[4-[(1,3-benzodioxol-5-yl)methyl]phenoxy]ethyl]-pyrrolidine;
2-[4-[2-(1-pyrrolidinyl)ethoxy]phenylmethyl]quinoline;
3-[4-[2-(1-pyrrolidinyl)ethoxy]phenylmethyl]quinoline;
25 1-[2-[4-[(2-thiophenyl)methyl]phenoxy]ethyl]pyrrolidine;
1-[2-[4-[(3-thiophenyl)methyl]phenoxy]ethyl]pyrrolidine;
1-[2-[4-[(2-furanyl)methyl]phenoxy]ethyl]pyrrolidine;
1-[2-[4-[(3-furanyl)methyl]phenoxy]ethyl]pyrrolidine;
2-[[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]methyl]pyridine;
30 1-[2-[4-[(4-fluorophenyl)methyl]phenoxy]ethyl]-pyrrolidine;
1-[2-[4-[(4-chlorophenyl)methyl]phenoxy]ethyl]-pyrrolidine;
1-[2-[4-[(2-fluorophenyl)methyl]phenoxy]ethyl]-pyrrolidine;
35 1-[2-[4-[(3-fluorophenyl)methyl]phenoxy]ethyl]-pyrrolidine;

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- 1-[2-[4-[(3-chlorophenyl)methyl]phenoxy]ethyl]-
pyrrolidine;
1-[2-[[5-(phenylmethyl)pyridin-2-yl]oxy]ethyl]-4-
piperidine-carboxamide;
- 5 1-[2-[4-(2-naphthalenyl)methoxy]phenoxyethyl]-
pyrrolidine;
3-[4-[2-(1-pyrrolidinyl)ethoxy]phenoxyethyl]quinoline;
2-methyl-4-[[4-[2-(1-pyrrolidinyl)ethoxy]phenoxy]-
methyl]thiazole;
- 10 1-[2-[4-[(4-bromophenyl)methoxy]phenoxy]ethyl]-
pyrrolidine;
1-[2-[4-[(2,6-dichlorophenyl)methoxy]phenoxy]ethyl]-
pyrrolidine;
1-[2-[4-[(4-fluorophenyl)methoxy]phenoxy]ethyl]-
pyrrolidine;
- 15 1-[2-[4-[(3-chlorophenyl)methoxy]phenoxy]ethyl]-
pyrrolidine;
1-[2-[4-[(2-fluorophenyl)methoxy]phenoxy]ethyl]-
pyrrolidine;
- 20 1-[2-[4-[(2-chlorophenyl)methoxy]phenoxy]ethyl]-
pyrrolidine;
1-[2-[4-[(3-trifluoromethyl)phenyl)methoxy]phenoxy]-
ethyl]-pyrrolidine;
1-[2-[4-[(2-methylphenyl)methoxy]phenoxy]ethyl]-
pyrrolidine;
- 25 1-[2-[4-[(3-fluorophenyl)methoxy]phenoxy]ethyl]-
pyrrolidine;
1-[2-[4-[(4-methylphenyl)methoxy]phenoxy]ethyl]-
pyrrolidine;
- 30 1-[2-[4-[(4-methoxyphenyl)methoxy]phenoxy]ethyl]-
pyrrolidine;
1-[2-[4-[(1-naphthyl)methoxy]phenoxy]ethyl]pyrrolidine;
1-[2-[4-[(2-thiophenyl)methoxy]phenoxy]ethyl]-
pyrrolidine;
- 35 methyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-2S-
pyrrolidine-2-carboxylate, monohydrochloride, hydrate;

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- 1-[3-[4-(phenylmethyl)phenoxy]propyl]-4-piperidine-carboxamide;
- N-[1-[2-[4-(phenylmethyl)phenoxy]ethyl]pyrrolidin-3-yl]acetamide, monohydrochloride;
- 5 phenylmethyl 1-[3-[4-(phenylmethyl)phenoxy]propyl]-L-prolinate;
- 1-[2-[4-[(2-thiophenyl)methyl]phenoxy]ethyl]-4-piperidine-carboxamide;
- 1-[2-[4-[(3-thiophenyl)methyl]phenoxy]ethyl]-4-piperidine-carboxamide;
- 10 1-[2-[4-[(2-thiazolyl)methyl]phenoxy]ethyl]-4-piperidine-carboxamide;
- 1-[2-[4-[(4-methoxyphenyl)methyl]phenoxy]ethyl]-4-piperidine-carboxamide;
- 15 1-[2-[4-[(4-fluorophenyl)methyl]phenoxy]ethyl]-4-piperidine-carboxamide;
- N-[1-[2-[4-(phenylmethyl)phenoxy]ethyl]piperidin-4-yl]-acetamide;
- N-[2-[4-(phenylmethyl)phenoxy]ethyl]cyclohexanamine, monohydrochloride;
- 20 N-[2-[4-(phenylmethyl)phenoxy]ethyl]cyclopentanamine, monohydrochloride;
- 1-[2-[4-(phenylmethyl)phenoxy]ethyl]piperidine-4-carboxamide;
- 25 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-3-piperidine-carboxamide;
- 1-[3-[4-(phenylmethyl)phenoxy]propyl]-3-piperidine-carboxamide;
- ethyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidine-carboxylate, monohydrochloride;
- 30 8-[2-[4-(phenylmethyl)phenoxy]ethyl]-1,4-dioxo-8-azaspiro[4.5]-decane, monohydrochloride;
- 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinol, monohydrochloride;
- 35 N-[1-[2-[4-(phenylmethyl)phenoxy]ethyl]piperidin-4-yl]-2-benzo[b]furancarboxamide;

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ethyl 3-[[[1-[2-[4-(phenylmethyl)phenoxy]ethyl]-
piperidine-4-yl]-carbonyl]amino]propanoate;
1-[3-(4-phenoxyphenoxy)propyl]-3-piperidinecarboxamide;
1-[3-(4-phenoxyphenoxy)propyl]-4-piperidinecarboxamide;
5 1-[2-(4-phenoxyphenoxy)ethyl]-4-piperidinecarboxamide;
1-[2-(4-phenoxyphenoxy)ethyl]-3-piperidinecarboxamide;
ethyl 1-[2-(4-phenoxyphenoxy)ethyl]-4-piperidine-
carboxylate, monohydrochloride;
N-methyl-1-[2-(4-phenoxyphenoxy)ethyl]-4-piperidine-
10 carboxamide;
4-[2-[4-(phenylmethyl)phenoxy]ethyl]morpholine,
monohydrochloride;
1-[3-[4-(phenylmethyl)phenoxy]propyl]pyrrolidine;
1,1-dimethylethyl 1-[3-[4-(phenylmethyl)phenoxy]-
15 propyl]-L-prolinate;
phenylmethyl 3-[[3-[4-(phenylmethyl)phenoxy]propyl]-
amino]propanoate;
methyl 4-oxo-1-[3-[4-(phenylmethyl)phenoxy]propyl]-
piperidine-3-carboxylate;
20 1,1-dimethylethyl 1-[3-[4-(phenylmethyl)phenoxy]-
propyl]piperidine-4-carboxylate;
ethyl N-[3-[4-(phenylmethyl)phenoxy]propyl]glycinate;
ethyl 3-[[3-[4-(phenylmethyl)phenoxy]propyl]amino]-
propanoate;
25 phenylmethyl 3-[[2-[4-(phenylmethyl)phenoxy]ethyl]-
amino]propanoate;
methyl 3-[[3-[4-(phenylmethyl)phenoxy]propyl]amino]-
propanoate;
1,1-dimethylethyl 3-[[3-[4-(phenylmethyl)phenoxy]-
30 propyl]amino]propanoate;
ethyl 1-[3-[4-(phenylmethyl)phenoxy]propyl]piperidine-
3-carboxylate;
ethyl 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-3-piperidine
carboxylate;
35 ethyl beta-[[2-[4-(phenylmethyl)phenoxy]ethyl]amino]-3-
pyridinepropanoate;

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- ethyl 3-[4-[4-(phenylmethyl)phenoxy]butylamino]-
propanoate;
phenylmethyl 3-[[4-[4-(phenylmethyl)phenoxy]butyl]-
amino]-propanoate;
5 ethyl 3-[[5-[4-(phenylmethyl)phenoxy]pentyl]amino]-
propanoate;
methyl 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-3-
pyrrolidineacetate;
methyl 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-3-
10 pyrrolidinecarboxylate;
1-[hexahydro-4-[2-[4-(phenylmethyl)phenoxy]ethyl]-
pyrazin-1-yl]-ethanone, monohydrochloride;
1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidine-
carbonitrile, monohydrochloride;
15 1-[[2,3-dihydro-5-(phenylmethyl)benzofuran-2-yl]-
methyl]-4-piperidinecarboxamide;
ethyl 1-[[2,3-dihydro-5-(phenylmethyl)benzo[b]furan-2-
yl]methyl]-4-piperidine carboxylate, monohydrochloride;
(+)-1-[[2,3-dihydro-2-methyl-5-(phenylmethyl)benzo[b]-
20 furan-2-yl]methyl] pyrrolidine, monohydrochloride;
(+)-1-[[2,3-dihydro-3-methyl-5-(phenylmethyl)benzo[b]-
furan-2-yl]methyl]-4-piperidinecarboxamide;
2,3-dihydro-5-(phenylmethyl)-2-(1-pyrrolidinylmethyl)-
furo[2,3-b]-pyridine, dihydrochloride;
25 (+)-1-[[5-(phenylmethyl)furo[2,3-b]pyridin-2-yl]-
methyl]-4-piperidine carboxamide;
1-[[2,3-dihydro-5-phenoxybenzo[b]furan-2-yl]methyl]-
pyrrolidine, monohydrochloride;
1-[[2,3-dihydro-5-phenoxybenzo[b]furan-2-yl]methyl]-4-
30 piperidinecarboxamide;
ethyl 1-[(2,3-dihydro-5-phenoxybenzo[b]furan-2-yl)-
methyl]-4-piperidinecarboxylate, monohydrochloride;
(+)-1-[[3,4-dihydro-6-(phenylmethyl)-2H-
benzopyran-2-yl]methyl]-4-piperidine, monohydrochloride
35 carboxamide;
1-[[2,3-dihydro-5-(phenylmethyl)benzo[b]furan-2-yl]-
methyl]-N-methyl-4-piperidine carboxamide;

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- 1-[(2,3-dihydro-5-phenoxybenzo[b]furan-2-yl)methyl]-N-methyl-4-piperidinecarboxamide;
2S-alpha-methyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-alpha-pyridinecarboxamide;
5 N-methyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinecarboxamide;
[[2,3-dihydro-5-(phenylmethyl)benzofuran-2-yl)methyl]-1-pyrazinecarboxamide;
4-[2-[4-(phenylmethyl)phenoxy]ethyl]-4H-imidazo[4,5-b]-
10 pyridine;
1-[2-[4-(phenylmethyl)phenoxy]ethyl]-1H-imidazo[4,5-b]-pyridine;
3-[2-[4-(phenylmethyl)phenoxy]ethyl]-3H-imidazo[4,5-b]-pyridine;
15 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-1H-benzimidazole;
5-[2-[4-(phenylmethyl)phenoxy]ethyl]-5H-imidazo[4,5-c]-pyridine, hydrate;
1-[2-[4-(phenylmethyl)phenoxy]ethyl]-1H-imidazo[4,5-c]-pyridine;
20 3-[2-[4-(phenylmethyl)phenoxy]ethyl]-3H-imidazo[4,5-c]-pyridine;
3-[3-[4-(phenylmethyl)phenoxy]propyl]-3H-imidazo[4,5-b]pyridine;
1-[3-[4-(phenylmethyl)phenoxy]propyl]-1H-imidazo[4,5-b]
25 pyridine;
1-[2-[4-(phenylmethyl)phenoxy]ethyl]-1H-pyrrolol[3,2-b]pyridine;
1-[3-(4-phenoxyphenoxy)propyl]-1H-benzimidazole;
1-[2-(4-phenoxyphenoxy)ethyl]-1H-benzimidazole;
30 1-[2-[4-(phenylmethoxy)phenoxy]ethyl]-1H-benzimidazole;
3-[2-[4-(phenylmethoxy)phenoxy]ethyl]-3H-imidazo[4,5-b]pyridine;
1-[2-[4-(phenylmethoxy)phenoxy]ethyl]-1H-imidazo[4,5-b]pyridine;
35 4-[2-[4-(phenylmethoxy)phenoxy]ethyl]-4H-imidazo[4,5-b]pyridine;

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- 3-[2-[4-(phenylmethoxy)phenoxy]ethyl]-3H-imidazo[4,5-c]
pyridine;
1-[2-[4-(phenylmethoxy)phenoxy]ethyl]-1H-imidazo[4,5-c]
pyridine;
5 5-[2-[4-(phenylmethoxy)phenoxy]ethyl]-5H-imidazo[4,5-c]
pyridine;
3-[2-(4-phenoxyphenoxy)ethyl]-3H-imidazo[4,5-b]pyridine;
1-[2-(4-phenoxyphenoxy)ethyl]-1H-imidazo[4,5-b]pyridine;
4-[2-(4-phenoxyphenoxy)ethyl]-4H-imidazo[4,5-b]pyridine;
10 5-[2-(4-phenoxyphenoxy)ethyl]-5H-imidazo[4,5-c]pyridine;
1-[2-(4-phenoxyphenoxy)ethyl]-1H-imidazo[4,5-c]pyridine;
3-[2-(4-phenoxyphenoxy)ethyl]-3H-imidazo[4,5-c]pyridine;
3-[3-(4-phenoxyphenoxy)propyl]-3H-imidazo[4,5-b]-
pyridine;
15 1-[3-(4-phenoxyphenoxy)propyl]-1H-imidazo[4,5-b]-
pyridine;
4-[3-(4-phenoxyphenoxy)propyl]-4H-imidazo[4,5-b]-
pyridine;
3-[3-(4-phenoxyphenoxy)propyl]-3H-imidazo[4,5-c]-
20 pyridine;
1-[3-(4-phenoxyphenoxy)propyl]-1H-imidazo[4,5-c]-
pyridine;
5-[3-(4-phenoxyphenoxy)propyl]-5H-imidazo[4,5-c]-
pyridine;
25 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-1H-imidazole,
monohydrochloride;
2,3,6,7-tetrahydro-1,3-dimethyl-7-[2-[4-(phenylmethyl)-
phenoxy]ethyl]-1H-purine-2,6-dione;
3-[2-[4-(4-fluorophenoxy)phenoxy]ethyl]-3H-imidazo-
30 [4,5-b]pyridine;
1-[2-[4-(4-fluorophenoxy)phenoxy]ethyl]-1H-imidazo-
[4,5-b]pyridine;
3-[2-[4-(4-fluorophenoxy)phenoxy]ethyl]-3H-imidazo-
[4,5-c]pyridine;
35 1-[2-[4-(4-fluorophenoxy)phenoxy]ethyl]-1H-imidazo-
[4,5-c]pyridine;

- 5-[2-[4-(4-fluorophenoxy)phenoxy]ethyl]-5H-imidazo-
[4,5-c]pyridine;
3-[3-[4-(phenylmethyl)phenoxy]propyl]-3H-imidazo[4,5-c]
pyridine;
5 1-[3-[4-(phenylmethyl)phenoxy]propyl]-1H-imidazo[4,5-c]
pyridine;
5-[3-[4-(phenylmethyl)phenoxy]propyl]-5H-imidazo[4,5-c]
pyridine;
7-[2-[4-(phenylmethyl)phenoxy]ethyl]-7H-purine;
10 9-[2-[4-(phenylmethyl)phenoxy]ethyl]-9H-purine;
1-[2-[4-(phenylmethyl)phenoxy]ethyl]-1H-purine;
3-[2-[4-(phenylmethyl)phenoxy]ethyl]-3H-purine,
monohydrochloride;
3-[[2,3-dihydro-5-(phenylmethyl)benzo[b]furan-2-yl]-
15 methyl]-3H-imidazo[4,5-b]pyridine, monohydrochloride;
1-[[2,3-dihydro-5-(phenylmethyl)benzo[b]furan-2-yl]-
methyl]-1H-imidazo[4,5-b]pyridine;
4-[[2,3-dihydro-5-(phenylmethyl)benzo[b]furan-2-yl]-
methyl]-4H-imidazo[4,5-b]pyridine, hydrochloride;
20 3-[[2,3-dihydro-5-(phenylmethyl)benzo[b]furan-2-yl]-
methyl]-3H-1,2,3-triazolo[4,5-b]pyridine;
2-[[2,3-dihydro-5-(phenylmethyl)benzo[b]furan-2-yl]-
methyl]-2H-1,2,3-triazolo[4,5-b]pyridine;
1-[[2,3-dihydro-5-(phenylmethyl)benzo[b]furan-2-yl]-
25 methyl-1H-1,2,3-triazolo[4,5-b]pyridine;
2-[[2,3-dihydro-5-(phenylmethyl)benzo[b]furan-2-yl]-
methyl]-2H-1,2,3-triazolo[4,5-c]pyridine,
monohydrochloride;
1-[[2,3-dihydro-5-(phenylmethyl)benzo[b]furan-2-yl]-
30 methyl]-1H-1,2,3-triazolo[4,5-c]pyridine,
monohydrochloride;
1-[2-[4-(phenylmethyl)phenoxy]ethyl]-1H-benzimidazole-
5-amine;
1-[2-[4-(phenylmethyl)phenoxy]ethyl]-1H-benzimidazole-
35 6-amine;
1-[2-[4-(phenylmethyl)phenoxy]ethyl]-1H-imidazo[4,5-b]-
pyridinium 4-oxide;

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- 3-[2-[4-(phenylmethyl)phenoxy]ethyl]-3H-imidazo[4,5-c]-pyridinium, 5-oxide;
1-[2-[4-(phenylmethyl)phenoxy]ethyl]-1H-imidazo[4,5-c]-pyridinium, 5-oxide;
- 5 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-2-pyrrolidine-methanol, monohydrochloride;
1-[2-[4-(phenylmethyl)phenoxy]ethyl]-3-pyrrolidinol;
hexahydro-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-1H-azepine, monohydrochloride;
- 10 1-[2-[4-(phenylmethyl)phenoxy]ethyl]azocine, monohydrochloride;
2,5-dimethyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-pyrrolidine, monohydrochloride;
2S-(methoxymethyl)-1-[2-[4-(phenylmethyl)phenoxy]-ethyl]pyrrolidine, monohydrochloride;
- 15 1-[2-[4-(phenylmethyl)phenoxy]ethyl]piperidine, monohydrochloride;
2,6-dimethyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-piperidine, monohydrochloride;
- 20 1-[2-[4-(phenylmethyl)phenoxy]propyl]piperidine, monohydrochloride;
hexahydro-1-[2-[4-(phenylmethyl)phenoxy]propyl]-1H-azepine, monohydrochloride;
[2-[4-(phenylmethyl)phenoxy]butyl]pyrrolidine, monohydrochloride;
- 25 2-[4-(phenylmethyl)phenoxy]ethyl]-1-[2-phenylmethyl]-pyrrolidine, monohydrochloride;
ethyl beta-[[3-[4-(phenylmethyl)phenoxy]propyl]amino]-4-pentynoate;
- 30 ethyl beta-[[2-[4-(phenylmethyl)phenoxy]ethyl]amino]-4-pentynoate;
phenylmethyl 3-[[3-[4-(phenylmethyl)phenoxy]propyl](2-propenyl)amino]propanoate;
ethyl [[4-[4-(phenylmethyl)phenoxy]butyl]-
- 35 (2-propenyl)amino]propanoate;
ethyl 3-[methyl-[3-[4-(phenylmethyl)phenoxy]propyl]-amino]propanoate;

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- methyl 3-[methyl[3-[4-(phenylmethyl)phenoxy]propyl]-amino]propanoate, hydrate;
ethyl 3-[[3-[4-(phenylmethyl)phenoxy]propyl](pyridin-3-ylmethyl)amino]propanoate;
5 ethyl [methyl[4-[4-(phenylmethyl)phenoxy]butyl]amino]-propanoate, triethylamine salt;
1,1-dimethyl-3-[[3-[4-(phenylmethyl)phenoxy]propyl]amino]propanol;
phenylmethyl 2,2-dimethyl-3-[methyl[3-[4-(phenylmethyl)phenoxy]propyl]amino]propanoate;
10 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidine-carboxylic acid hydrazide;
N-[2-(aminocarbonyl)ethyl]-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinecarboxamide;
15 N-methyl-3-[[3-[4-(phenylmethyl)phenoxy]propyl]amino]-propanamide;
3-[[3-[4-(phenylmethyl)phenoxy]propyl]amino]propanamide;
1-(4-morpholinyl)-3-[[3-[4-(phenylmethyl)phenoxy]propyl]amino]-1-propanone;
20 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-3-pyrrolidine-carboxamide;
1-[2-[4-(phenylmethyl)phenoxy]ethyl]-3-pyrrolidine-acetamide;
[1-[2-[4-(phenylmethyl)phenoxy]ethyl]-2S-pyrrolidin-2-yl]methyl N-phenylcarbamate;
25 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidine-carboxylic acid, monohydrochloride, hydrate;
1-[3-[4-(phenylmethyl)phenoxy]propyl]-2S-pyrrolidine-2-carboxylic acid;
30 3-[[3-[4-(phenylmethyl)phenoxy]propyl]amino]propanoic acid;
2-methyl-3-[methyl[3-[4-(phenylmethyl)propyl]amino]-propanoic acid;
3-[[4-[4-(phenylmethyl)phenoxy]butyl]amino]propanoic
35 acid;
3-[methyl[3-[4-(phenylmethyl)phenoxy]propyl]amino]-propanoic acid;

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- 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-3-pyrrolidinamine,
dihydrochloride;
N-[1-[2-[4-(phenylmethyl)phenoxy]ethyl]pyrrolidin-3-yl]
urea;
- 5 alpha-chloro-N-[1-[2-[4-(phenylmethyl)phenoxy]ethyl]pyr-
rolidin-3-yl]acetamide, monohydrochloride;
1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinamine;
N-[1-[2-[4-(phenylmethyl)phenoxy]ethyl]piperidin-4-yl]-
urea;
- 10 hexahydro-1-[2-[4-(phenylmethyl)phenoxy]ethyl]pyrazine,
dihydrochloride;
hexahydro-4-[2-[4-(phenylmethyl)phenoxy]ethyl]-
1-pyrazinethioamide;
hexahydro-4-[2-[4-(phenylmethyl)phenoxy]ethyl]-
15 1-pyrazinecarboxamide;
hexahydro-1-methylsulfonyl-4-[2-[4-(phenylmethyl)-
phenoxy]ethyl]pyrazine;
N-[2-alpha-methyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-
piperidin-4-beta-yl]acetamide;
- 20 4-hydroxy-cis-2-methyl-1-[2-[4-(phenylmethyl)phenoxy]-
ethyl]piperidine, monohydrochloride;
2-[4-(phenylmethyl)phenoxy]ethanamine,
monohydrochloride;
(±)ethyl 2-methyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-
25 piperidine-4-carboxylate;
phenylmethyl 3-[[3-(4-phenoxyphenoxy)propyl]amino]-
propanoate;
phenylmethyl 3-[methyl[3-(4-phenoxyphenoxy)propyl]-
amino]propanoate;
- 30 methyl 8-[2-[4-(phenylmethyl)phenoxy]ethyl]-8-
azabicyclo[3.2.1]octane-3-carboxylate;
3-[[3-(4-phenoxyphenoxy)propyl]amino]propanoic acid;
ethyl 1-[2-(4-phenoxyphenoxy)ethyl]piperidine-4-
acetate, monohydrochloride;
- 35 ethyl 1-[2-[[5-(phenylmethyl)thien-2-yl]oxy]ethyl]-
piperidine-4-carboxylate;

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- 3-[methyl[3-(4-phenoxyphenoxy)propyl]amino]propanoic acid;
- phenylmethyl 3-[[4-(4-phenoxyphenoxy)butyl]amino]-propanoate;
- 5 5-[1-[2-[4-(phenylmethyl)phenoxy]ethyl]piperidin-4-yl]-1H-tetrazole;
- (cis)-2R,6-dimethyl-1-[2-[4-(phenylmethyl)phenoxy]-ethyl]piperidine-4-carboxamide;
- 3-[[4-(4-phenoxyphenoxy)butyl]amino]propanoic acid;
- 10 ethyl 1-[2-[4-[[3-fluorophenyl)methyl]phenoxy]ethyl]-piperidine-4-carboxylate;
- ethyl 1-[2-[4-(2-thienylmethyl)phenoxy]ethyl]-piperidine-4-carboxylate;
- 3-[[3-[4-[(4-fluorophenyl)methyl]phenoxy]propyl]-methylamino]propanoic acid, monohydrochloride;
- 15 methyl 3-[methyl[3-[4-(2-thienylmethyl)phenoxy]propyl]-amino]propanoate;
- 3-[methyl[3-[4-(2-thienylmethyl)phenoxy]propyl]amino]-propanoic acid, monohydrochloride;
- 20 1-[2-(4-phenoxyphenoxy)ethyl]piperidine-4-carboxylic acid, monohydrochloride;
- methyl 3-[3-[4-[(4-fluorophenyl)methyl]phenoxy]propyl]-methylamino]propanoate;
- ethyl 1-[2-[4-[(4-fluorophenyl)methyl]phenoxy]ethyl]-piperidine-4-carboxylate;
- 25 ethyl 1-[2-[4-(3-thienylmethyl)phenoxy]ethyl]-piperidine-4-carboxylate;
- methyl 3-[methyl[3-[4-(3-thienylmethyl)phenoxy]propyl]-amino]propanoate;
- 30 5-[2-methyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-piperidin-4-yl]-1H-tetrazole, monohydrate;
- methyl 3-[[3-[4-(4-fluorophenoxy)phenoxy]propyl]-methylamino]propanoate;
- 1-[2-[4-[(4-fluorophenyl)methyl]phenoxy]ethyl]-piperidine-4-carboxylic acid, monohydrochloride;
- 35 1-[2-[4-(3-thienylmethyl)phenoxy]ethyl]piperidine-4-carboxylic acid, monohydrochloride;

- 30 -

3-[methyl[3-[4-(3-thienylmethyl)phenoxy]propyl]amino]-
propanoic acid, monohydrochloride;
ethyl 1-[2-[4-(4-fluorophenoxy)phenoxy]ethyl]-
piperidine-4-carboxylate, monohydrochloride;
5 1-[2-[4-(4-fluorophenoxy)phenoxy]ethyl]piperidine-4-
carboxylic acid, monohydrochloride;
1-[2-[4-[(3-fluorophenyl)methyl]phenoxy]ethyl]-4-
carboxylic acid, monohydrochloride;
5-phenylmethyl-2-[2-(1-pyrrolidinyl)ethoxy]pyridine;
10 methyl(cis)-2R,6-dimethyl-1-[2-[4-(phenylmethyl)-
phenoxy]ethyl]piperidine-4-carboxylate;
ethyl 3-[[4-[4-phenoxyphenoxy]butyl]amino]propanoate;
1-[2-[4-(2-thienylmethyl)phenoxy]ethyl]piperidine-4-
carboxylic acid, monohydrochloride.

15 The compounds of the invention are prepared from
readily available starting materials by any of the
following alternate processes in a conventional manner.
The following reaction schemes describe methods which
can be employed for preparing the compounds of formula
20 I, including starting materials, intermediates and
reaction conditions. The following terms, as used
herein, have the definitions which are given in the
table below.

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DEFINITIONS

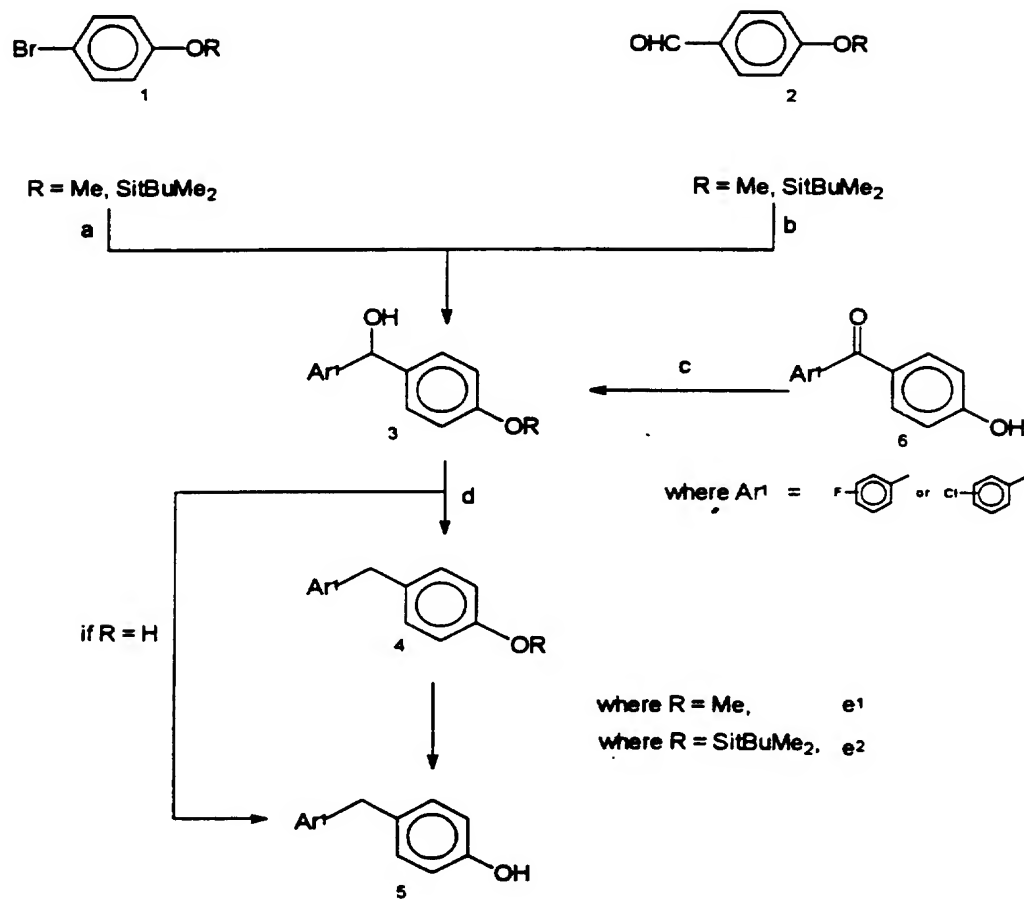
	NMMO	N-methylmorpholine-N-oxide
	Me	methyl
5	SitBuMe ₂	t-butyldimethylsilyl
	nBuLi	n-butyllithium
	THF	tetrahydrofuran
	Et ₂ O	diethyl ether
	EtOH	ethyl alcohol
10	Pd/C	palladium on carbon
	TFA	trifluoroacetic acid
	Et ₃ SiH	triethylsilane
	TBAF	tetrabutylammonium fluoride
	DMF	dimethylformamide
15	nBu ₄ NBr	tetra-n-butylammonium bromide
	TsCl	tosylchloride or p-toluenesulfonyl chloride
	TsO	tosylate or p-toluenesulfonate
	MeOH	methyl alcohol
20	AcOH	acetic acid
	Bn	benzyl
	DEAD	diethylazodicarboxylate
	Ph ₃ P	triphenylphosphine
	MCPBA	metachloroperbenzoic acid
25	LAH	lithium aluminum hydride
	TsOH	tosic acid or p-toluenesulfonic acid
	LDA	lithium diisopropylamide
	DSC	disuccinylcarbonate
	nBuOH	n-butyl alcohol
30	TFAA	trifluoroacetic anhydride
	Me ₃ SnN ₃	trimethyl-tin azide
	TMS	trimethyl silyl
	Ac ₂ O	acetic anhydride
	Ac	acetate
35	EtOAc	ethyl acetate
	Hep	heptane

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Preparation of the compounds of formula I may be accomplished via one or more of the synthetic schemes which are set forth hereinafter.

5 Schemes 1-4 depict various methods for preparing substituted phenols of the formula $\text{Ar}^1\text{-Q-Ar}^2\text{-OH}$, wherein Ar^1 and Ar^2 are independently phenyl, substituted phenyl, pyridyl or thienyl moieties.

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Scheme 1

- a) nBuLi , THF, -78°C ; Ar^1CHO .
 b) Ar^1Li or Ar^1MgBr , Et_2O , -78°C .
 c) EtOH , NaBH_4 .
 d) EtOH , 4% Pd/C , H_2 or CH_2Cl_2 , TFA, Et_3SiH .
 e1) BBR_3 , CH_2Cl_2 , -78°C .
 e2) THF, TBAF.

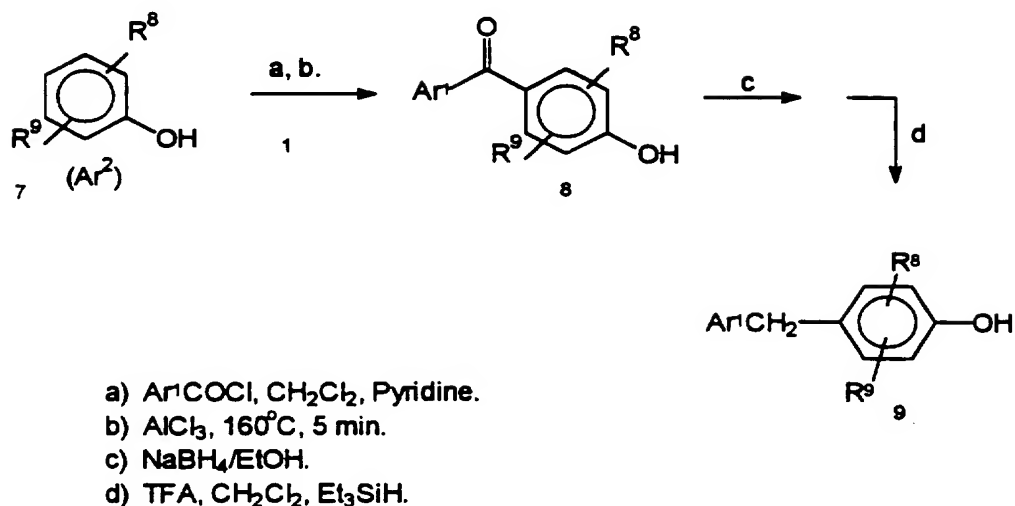
- 34 -

Scheme 1 shows methods for producing compounds of the formula $\text{Ar}^1\text{-CH}_2\text{-Ar}^2\text{-OH}$ wherein Ar^2 is a phenyl moiety. Scheme 1 shows two related precursor compounds (1, 2) which may be employed as a starting material.

5 Compound 1 is an alkylated or silylated derivative of p-bromophenol. A convenient starting material 1 is 1-bromo,4-methoxyphenol (i.e., R is methyl). On the other hand, compound 1 may be readily provided by silylation of p-bromophenol with t-butyldiphenylsilyl chloride or
10 other silylating agents (see, Example 2). In either event, compound 1 may be reacted with tert-butyl lithium in an ethereal solvent at low temperature, such as in THF at -78°C , and quenched with an arylaldehyde (Ar^1CHO) to yield compound 3. Similarly, starting from
15 compound 2, a p-methoxybenzaldehyde or a silylated derivative of p-hydroxybenzaldehyde (see, Example 1) may be employed. Compound 2 may be reacted with an aryl lithium (Ar^1Li) or aryl magnesium bromide (Ar^1MgBr) to yield compound 3. Regardless of which route is
20 chosen, compound 3 is reduced, e.g., by hydrogenation over palladium on carbon or with triethylsilane, to provide compound 4. Compound 4 is readily deprotected using TBAF in THF (desilylation) or using BBr_3 in methylene chloride at -78°C (dealkylation) to provide
25 compound 5.

Compounds 5 of the formula $\text{Ar}^1\text{-CH}_2\text{-Ar}^2\text{-OH}$, wherein Ar^1 is a para-halogen-substituted phenyl moiety, such compounds are preferably provided by sodium borohydride reduction of a compound 6 to provide compound 3,
30 followed by hydrogenation as described above to afford compound 5.

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Scheme 2

Scheme 2 depicts the preparation of compounds of
 5 formula $\text{Ar}^1\text{-CH}_2\text{-Ar}^2\text{-OH}$ wherein $\text{-Ar}^2\text{-OH}$ is a substituted
 phenol $\text{R}^8(\text{R}^9)\text{PhOH}$ and R^8 and R^9 are as defined
 hereinbefore. In this reaction sequence, the
 substituted phenol 7 is reacted with a suitable aryloyl
 chloride to give the intermediate aryloyl ester (not
 10 shown) which is heated to a temperature of about 160°C
 in the presence of AlCl_3 to promote Fries rearrangement
 which affords the desired compound 8, having the
 specifically substituted Ar^2 moiety. Compound 8 may be
 reduced utilizing the two-step reduction sequence
 15 (Scheme 1, steps (c) and (d)) to provide compound 9.

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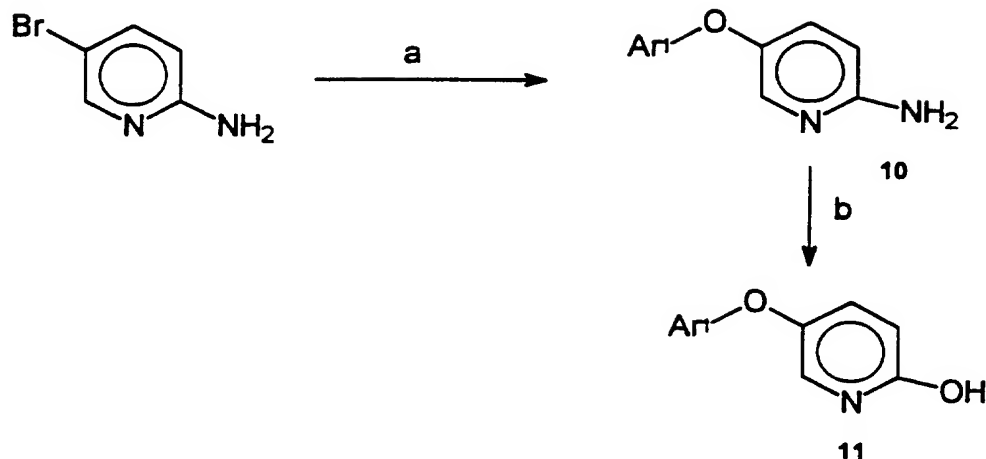
Scheme 3

5

- a) KOH, $\text{HAr}^2\text{-OMe}$, Cu^0 , 160°C .
b) CH_2CH_2 , BBr_3 , -78°C .

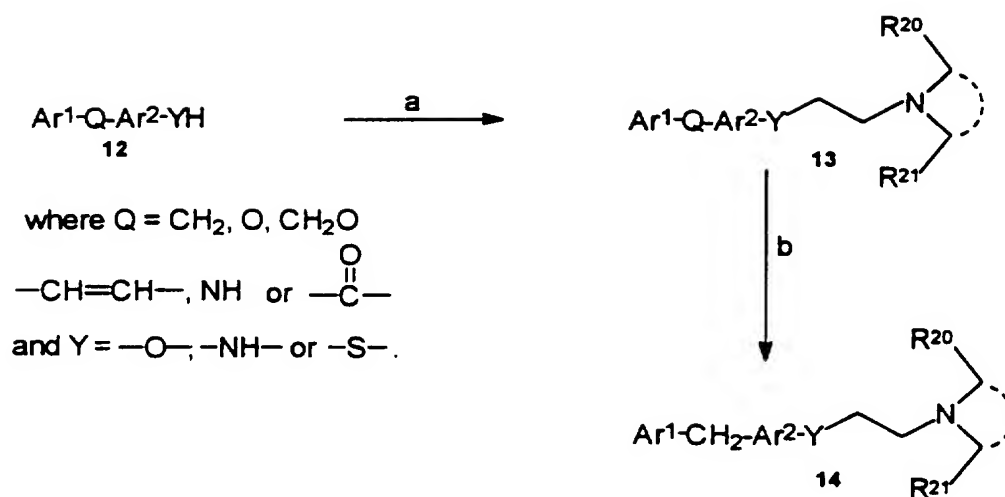
Scheme 3 shows a general method for the
10 preparation of phenols of the formula $\text{Ar}^1\text{-O-Ar}^2\text{-OH}$
wherein Ar^1 is a substituted phenol. Ar^1 may be any
substituted arylphenol which is capable of reacting
with 4-iodoanisole in an Ullman coupling reaction.
See, A. Moroz, et al., *Russ. Chem. Rev.* 43, 679 (1974).
15 The Ullman reaction is carried out conventionally in
the presence of activated copper or copper iodide at a
temperature of about 150°C to 200°C . A particularly
preferred substituted phenol for providing compounds of
the present invention having a substituted Ar^1 moiety is
20 4-fluorophenol.

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Scheme 4a) Ar¹OH, CuI, K₂CO₃.b) 4N-H₂SO₄, NaNO₂.

Scheme 4 shows a synthesis for making compounds of the formula Ar¹-O-pyridyl-OH (i.e., Ar² is pyridyl). In the reaction, 2-amino-5-bromopyridine is combined with an excess of a suitable phenol (Ar¹OH) and coupled utilizing the Ullman reaction, essentially as described with reference to Scheme 3, to provide the aminopyridine derivative 10. Compound 10 is diazotized with sodium nitrite/H₂SO₄/H₂O and decomposed to afford compound 11.

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Scheme 5a) Chloroethylaminoalkyl, DMF, K₂CO₃ - 50-80°C.b) where Q = $\text{--}\overset{\text{O}}{\parallel}\text{C--}$ 1) NaBH₄2) Et₃SiH

5

10

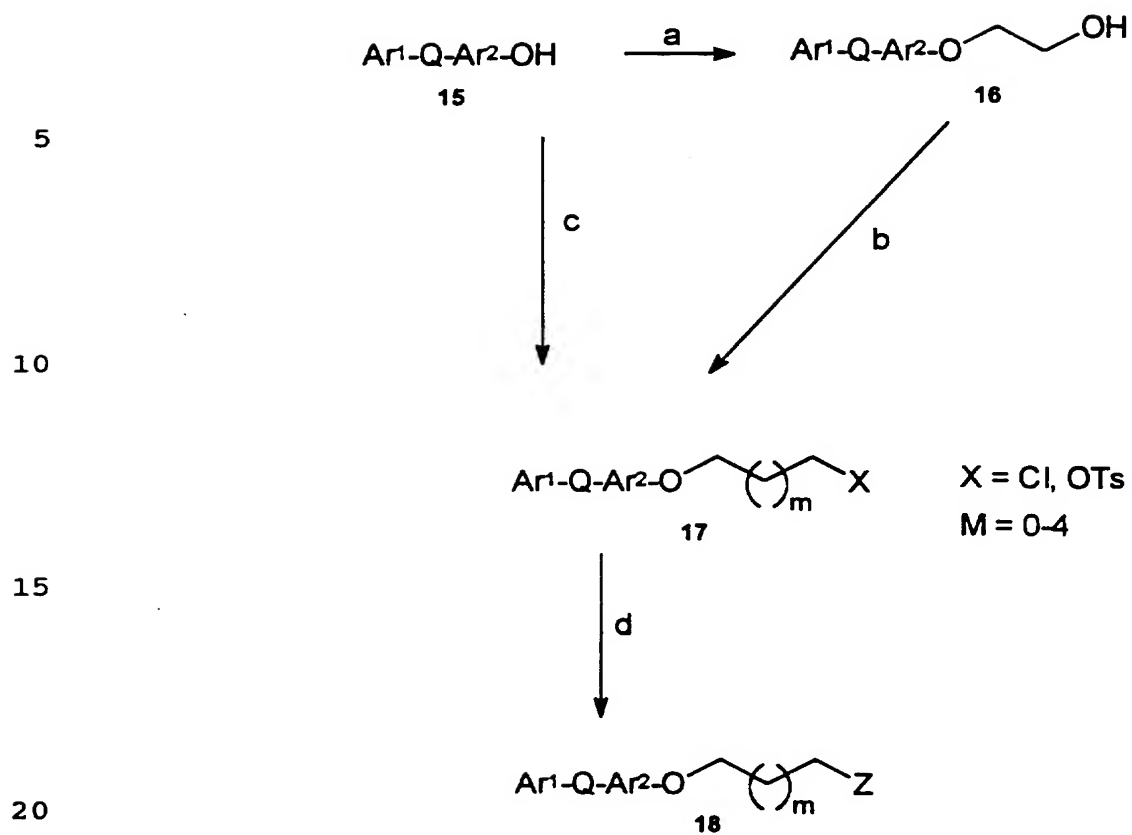
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Scheme 5 shows the preparation of compounds of the general formula $\text{Ar}^1\text{-Q-Ar}^2\text{-Y-R-Z}$ (Formula I) from compounds of the formula $\text{Ar}^1\text{-Q-Ar}^2\text{-YH}$ (12) (wherein R is ethylene, Y is -O-, -NH- or -S-, R^{20} and R^{21} are independently hydrogen or lower alkyl, and wherein Ar^1 , Q, Ar^2 , and Z are previously defined). Compounds of the formula $\text{Ar}^1\text{-Q-Ar}^2\text{-YH}$ may be made in accordance with Schemes 1-4 or may be obtained commercially, including 4-hydroxydiphenylmethane, 4-hydroxybenzophenone, 4-benzyloxyphenol, etc.

A compound of the formula $\text{Ar}^1\text{-Q-Ar}^2\text{-YH}$ (12) may be converted into a compound of the present invention via alkylation with any of a variety of chloroethylaminoalkyl analogs, wherein the aminoalkyl moiety may be cyclic or acyclic. Where Q is carbonyl, the carbonyl moiety of compound 13 is reduced to $-\text{CH}_2-$ as depicted in steps (c) and (d) of Scheme 1 to afford compound 14.

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Scheme 6a) Ethylene Carbonate, DMF, $n\text{Bu}_4\text{NBr}$, 140°C .b) TsCl, Pyridine, CH_2Cl_2 , 0°C ($m = 0$).c) NaH, DMF, $\text{Cl}-(\text{CH}_2)_m-\text{Br}$, 50°C .d) DMF, K_2CO_3 , ZH, wherein Z is defined hereinbefore.

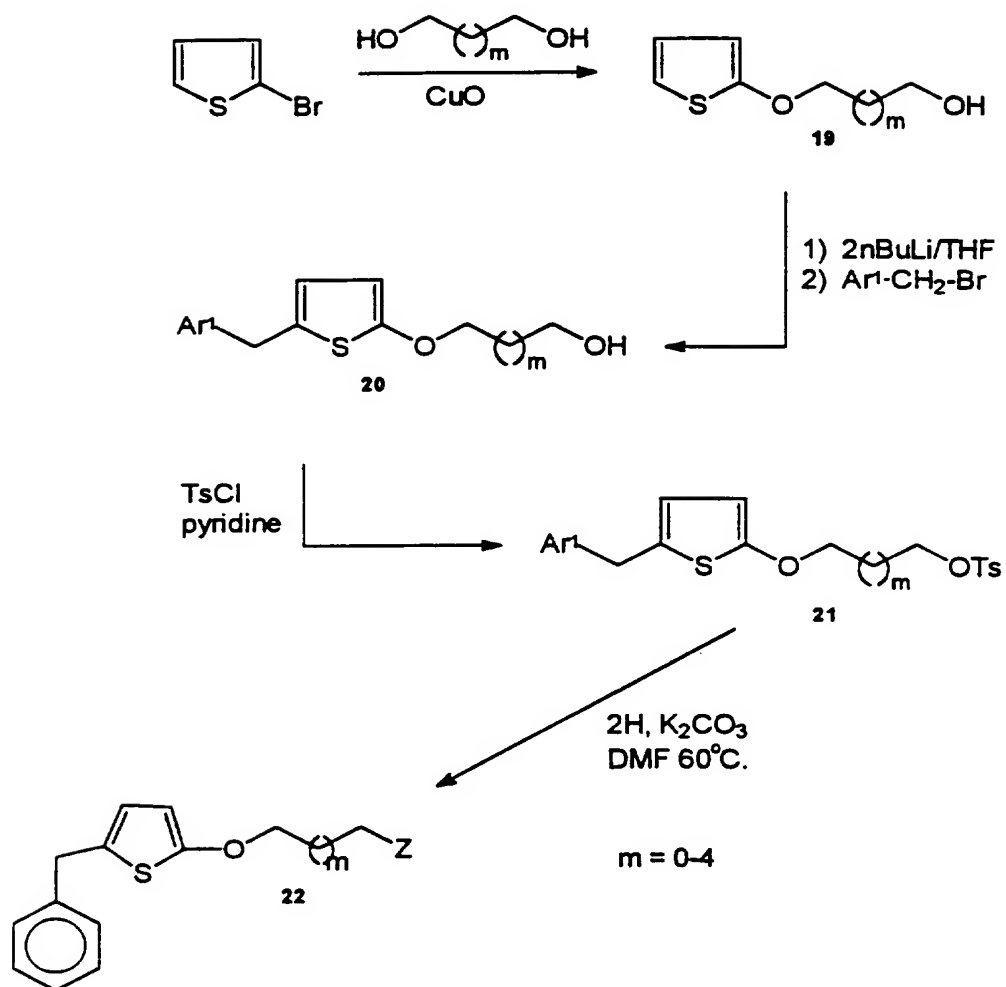
- 41 -

Scheme 6 shows a presently preferred method for preparing compounds of the formula $\text{Ar}^1\text{-Q-Ar}^2\text{-O-R-Z}$, wherein R is a linear alkylene moiety. Scheme 6 depicts alternate reaction pathways for adding an alkylene linker moiety, R (as defined in formula I) to the phenolic hydroxyl group of compound 15, which alkylene linker terminates in a reactive halogen or tosylate group. In the pathway which provides compound 17 wherein R is ethylene (i.e., R provides a 2 carbon linker) compound 15 is reacted with ethylene carbonate in DMF in the presence of nBu_4NBr to give compound 16 which is subsequently reacted with tosylchloride in dichloromethane and pyridine to provide compound 17 wherein X is -OTs.

Where R is a $\text{C}_3\text{-C}_6$ alkylene moiety, compound 15 is reacted with $\text{CH}_2\text{Cl-(CH}_2\text{)}_m\text{-CH}_2\text{Br}$ (wherein m is 1-4) in the presence of DMF and NaH to provide compound 17 wherein X is Cl.

Compound 17 is reacted with a nitrogen containing compound of the formula ZH in DMF at 60° in the presence of K_2CO_3 , to give compound 18, wherein Z is an acyclic amine moiety, a monocyclic or bicyclic amine moiety or a monocyclic or bicyclic heteroaromatic moiety as defined hereinbefore with reference to compounds of Formula I.

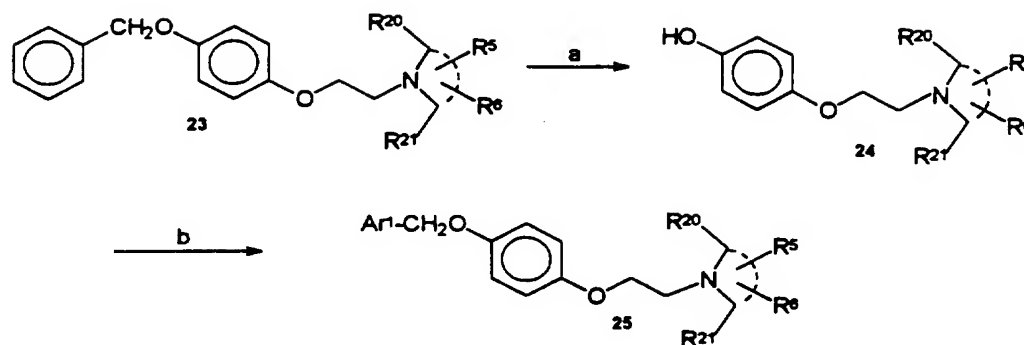
- 42 -

Scheme 7

- 43 -

Scheme 7 describes a method for making compounds of the Formula I wherein Ar² is thiophene. The synthesis entails reaction of 2-bromothiophene or 2-iodothiophene with a terminally substituted diol of the formula CH₂OH-(CH₂)_m-CH₂OH wherein m = 0-4. Such diols include ethylene glycol, 1,3 propanediol, 1,4 butanediol and 1,5 pentanediol and 1,6 hexanediol. The reaction is carried in the presence of copper (II) oxide in the diol as solvent at 120°C to afford compound 19. Compound 19 is lithiated on the thiophene ring with nBuLi (2 equivalents) in THF at -78°C to produce the corresponding 5-lithio anion of compound 19 which is then quenched with a suitable arylmethylbromide (Ar¹CH₂Br), for example, benzylbromide, to afford compound 20, which may be converted into compound of Formula I via tosylation followed by displacement as described in Scheme 6 (20 → 21 → 22).

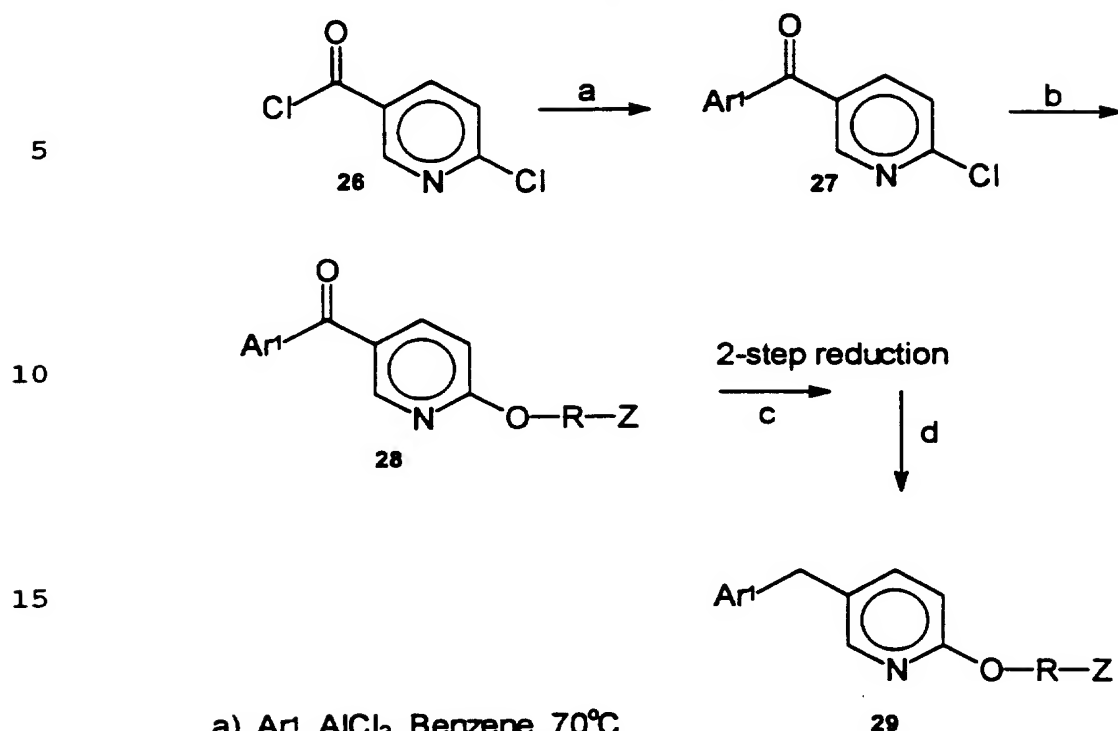
- 44 -

Scheme 8

a) H₂/4% Pd/C, EtOH.
 b) NaH, DMF, Ar¹-CH₂Br.

Scheme 8 describes the synthesis of compounds of
 5 Formula I wherein -Q-Ar²- is "-CH₂O-phenyl-" and Ar¹ may
 be any of a variety of aryl moieties (see, for
 example, Table 13). The synthesis starts with a
 compound of Formula I wherein Ar¹-Q- is Ph-CH₂-O- (23),
 and debenzylates the compound, employing H₂, 4% Pd/C,
 10 EtOH, to afford intermediate phenol 24 which is
 alkylated in the presence of NaH in DMF with any of a
 variety of arylmethylobromides to afford compound 25.
 Suitable arylmethylobromides include, but are not
 limited to the arylmethylobromides enumerated with
 15 reference to Scheme 7.

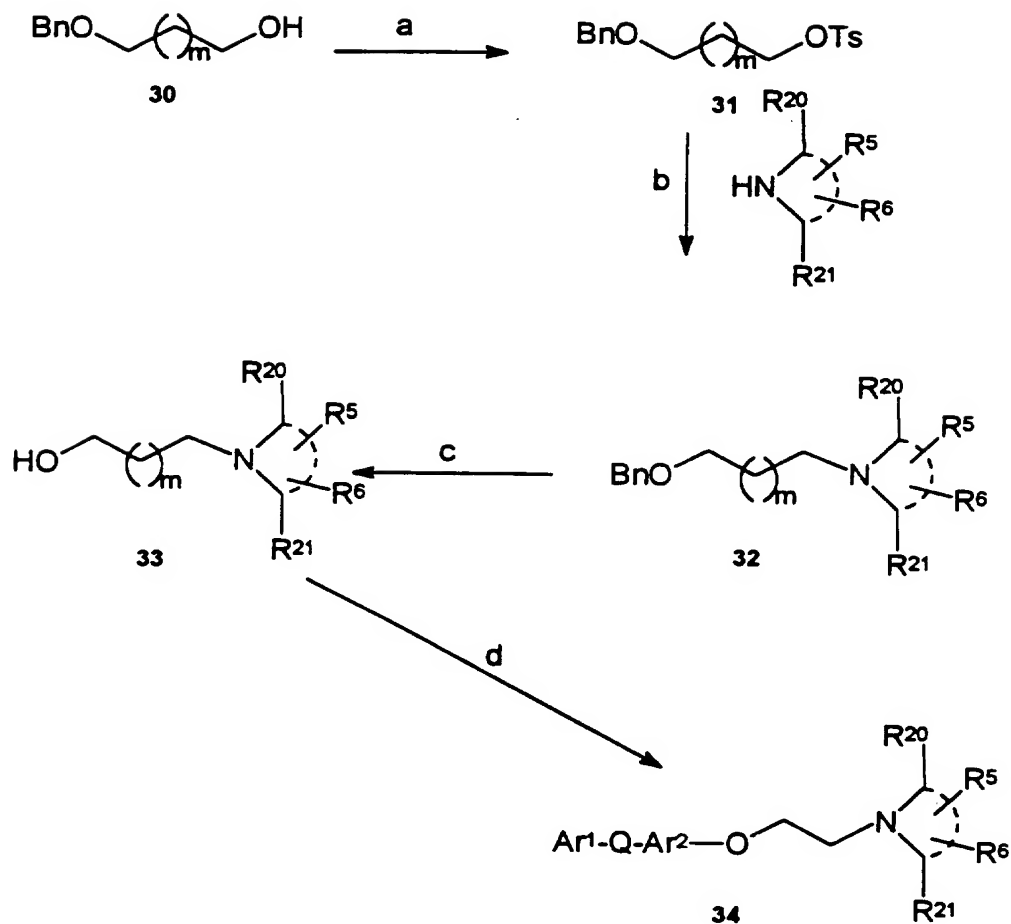
- 45 -

Scheme 9

- a) Ar¹, AlCl₃, Benzene, 70°C.
 b) HO-R-Z, Benzene, NaH.
 c) EtOH, NaBH₄.
 d) 4% Pd/C, MeOH/40%AcOH.

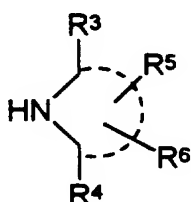
Scheme 9 generally depicts methods for preparing compounds of Formula I wherein Ar² is a 2,5-disubstituted pyridinyl moiety. Such compounds of the present invention may be prepared starting from the acid chloride of 2-chloro-5-pyridine-carboxylic acid. The acid chloride 26 is combined with a suitable aryl compound (Ar¹) and reacted under Friedel-Crafts acylation conditions to provide the chloropyridinyl containing ketone 27, which is reacted with a suitable hydroxyalkylamine of the formula HO-R-Z, wherein R and Z are as defined hereinbefore, to yield compound 28 which is subject to a 2-step reduction (shown in steps (c) and (d) of Scheme 1) to provide compound 29 which is a compound of Formula I.

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Scheme 10a) TsCl , Pyridine, CH_2Cl_2 b) DMF , K_2CO_3 c) H_2/Pd , EtOH d) $\text{Ar}^1\text{-Q-Ar}^2\text{-OH}$, DEAD , Ph_3P , THF .

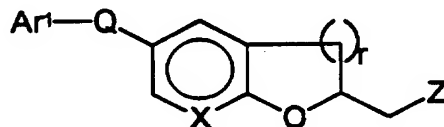
- 47 -

Scheme 10 describes preparation of a variety of compounds of the formula HO-R-Z 33 wherein R is alkylene and Z is defined hereinbefore. These compounds may be employed in the methods described in Scheme 9, step b. In Scheme 10, a benzyloxyalcohol 30 is converted into the corresponding tosylate 31 by reaction with tosylchloride in the presence of pyridine and methylene chloride at 0°C which is reacted with a secondary amine of the formula



in DMF at 60°C, in the presence of K_2CO_3 to provide compound 32. Compound 32 is hydrogenated [H_2/Pd , ethanol] to afford compounds of the formula HO-R-Z (33), wherein R is alkylene, and coupled to compounds of the formula Ar^1-Q-Ar^2-OH (see schemes 1-4) in the presence of diethylazodicarboxylate (DEAD) and triphenylphosphine in THF (O. Mitsunoba, *Synthesis*, 1, (1981)) to provide compound 34 which is a compound of Formula I.

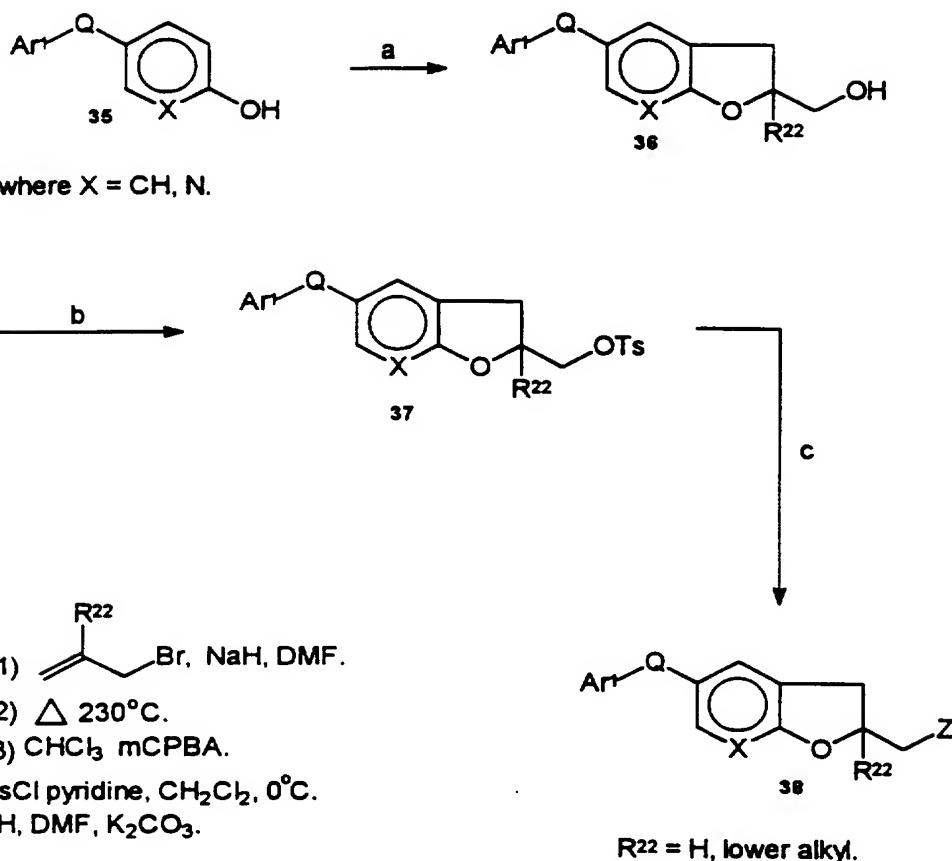
In another of its embodiments the present invention entails the compound of the formula



wherein r is 1 or 2, and Ar^1 , Q, X and Z are as defined hereinbefore. In this embodiment of the invention the compounds are rotationally constrained by fusion of a portion of the linker group R to the Ar^2 moiety through a 5- or 6-membered fused ring (i.e., dihydrobenzofuran or tetrahydrobenzopyran).

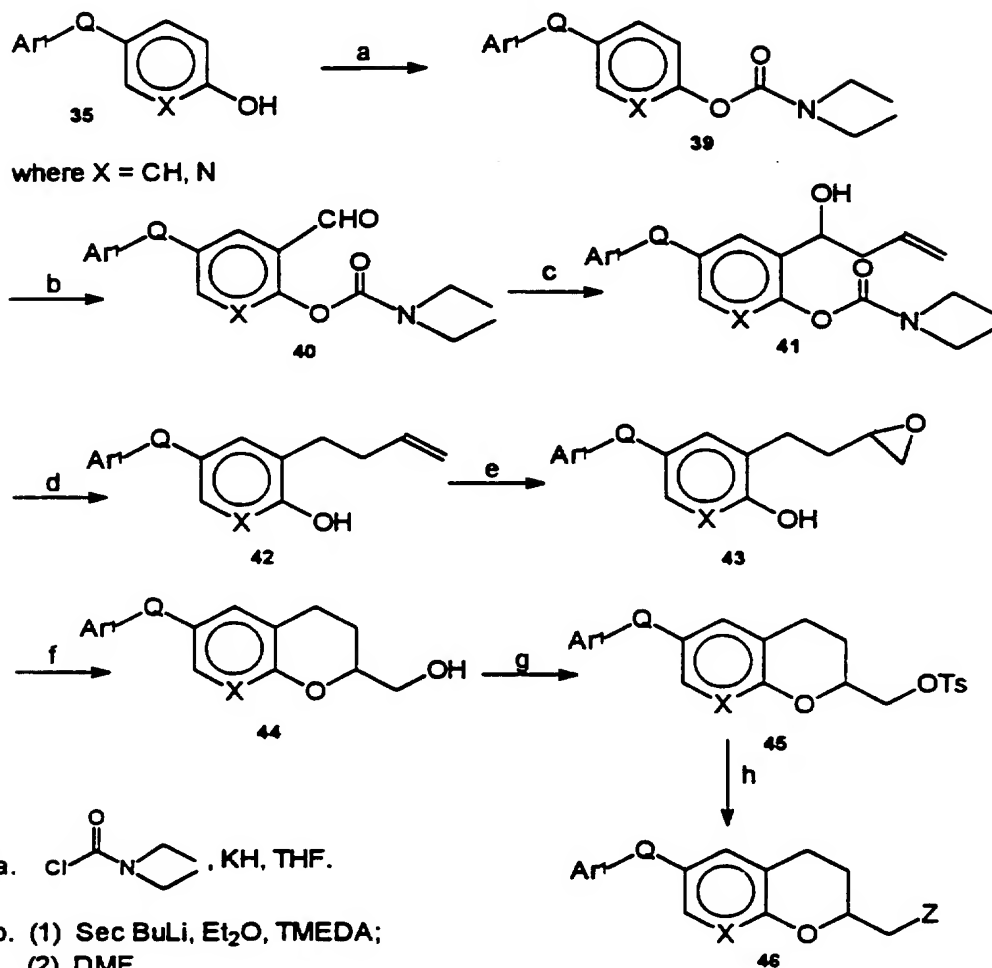
- 48 -

Scheme 11



With reference to Scheme 11, compound 35 is alkylated in DMF in the presence of sodium hydride with allylbromide or a 2-methyl substituted allylbromide to afford the corresponding O-allyl ether (not shown), which is heated to 230°C in a Claissen rearrangement reaction, followed by oxidative cyclization with metachloroperbenzoic acid (mCPBA) in chloroform to yield the alcohol 36. Alcohol 36 is reacted with tosyl chloride in pyridine/methylene chloride mixture at 0°C to afford the corresponding tosylate 37, which is then condensed (in DMF in the presence of potassium carbonate) with a primary or secondary amine, ZH, or an aromatic nitrogen containing heterocycle, ZH, wherein Z is define hereinbefore to afford compound 38 which is a compound of formula I.

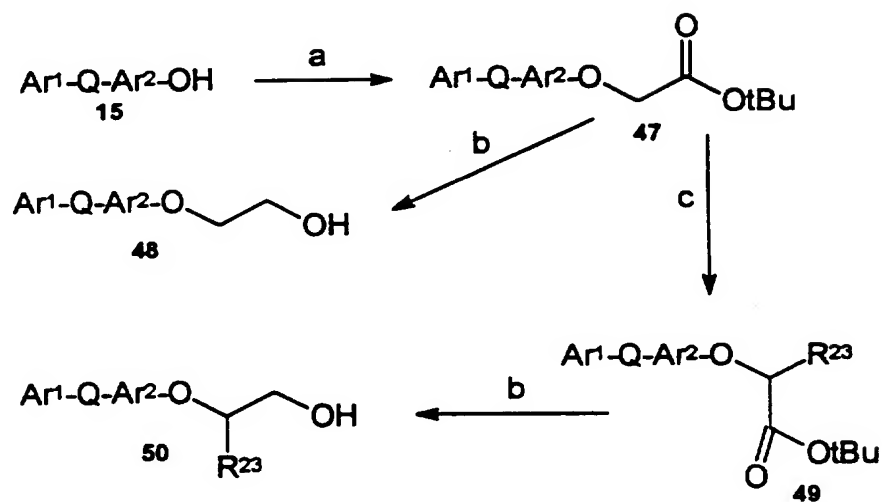
- 49 -

Scheme 12

- 50 -

Scheme 12 shows a method for preparing compounds of the present invention from phenols of the formula 35. Phenol 35 can be transformed into tetrahydrobenzopyran analogs via the following six-step (steps (a) -(f)) procedure. In step (a), the phenol 35 is converted into its corresponding diethylcarbamate 39 employing diethylcarbamoylchloride, KH, and DMF. In step (b), the diethylcarbamate compound 39 is then ortho-lithiated (sec.butyllithium, Et₂O, TMEDA) and quenched with DMF to afford aldehyde 40. The aldehyde 40 is reacted with allylmagnesium bromide in step (c) and the resulting alcohol 41 is reduced and deprotected in step (d) utilizing sulphur-trioxide/pyridine in THF, followed by addition of lithium aluminum hydride to afford phenol 42, which is substituted with but-3-ene in the position ortho to the phenolic hydroxyl. Phenol 42 is oxidatively cyclized in two steps, via epoxide 43 utilizing mCPBA in CHCl₃, followed by acid-catalyzed epoxide ring opening with tosic acid in CHCl₃ in step (f) to afford the tetrahydrobenzopyran containing alcohol 44. Alcohol 44 may be further converted into compounds of the formula I, via formation of the corresponding tosylate 45, followed by displacement with compounds of the formula ZH, as described in Scheme 6.

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Scheme 13

- a) THF, NaH, tButylbromoacetate.
b) THF, LAH.
c) THF, LDA, -78°C ; R^{23}X , wherein
 R^{23} is lower alkyl or benzyl and
X is Br or I.

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Scheme 13 represents an alternative procedure to that shown in Scheme 6 for attaching an hydroxyethylene moiety to phenols of the formula $\text{Ar}^1\text{-Q-Ar}^2\text{-OH}$ (15). In the methods depicted in Scheme 13, phenol 15 is

5 alkylated with t-butylbromoacetate in THF in the presence of sodium hydride to yield t-butyl ester 47, which is then reduced with LAH in THF to afford the hydroxyethylene substituted analogs, $\text{Ar}^1\text{-Q-Ar}^2\text{-O-CH}_2\text{CH}_2\text{-OH}$ 48.

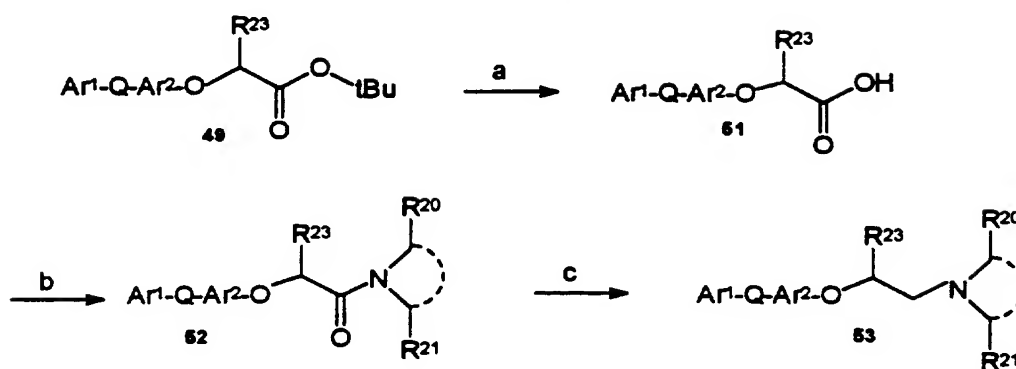
10 In an analogous reaction sequence, t-butyl ester 47 may be alpha-alkylated via reaction with LDA in THF at -78°C , followed by quenching with an alkylhalide (R^{22}X) at -78°C . The resulting alpha-substituted ester 49 is reduced (LAH in THF) to afford compound 50 having

15 a branched alkylene moiety.

The synthetic route described in Scheme 13 provides compounds which may be employed in steps (c) and (d) of Scheme 6 to provide compounds of Formula I having a linear or branched alkylene moiety.

20

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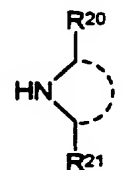
Scheme 14

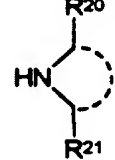
R = H, CH₃, CH₂CH₃ or benzyl

a) TFA, CH₂Cl₂, MeOH.

b) Disuccinylcarbonate, DMF, Pyridine,

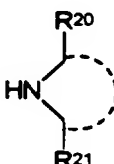
c) THF, LAH.



wherein HN  does not contain functionality
reactive towards LAH reduction.

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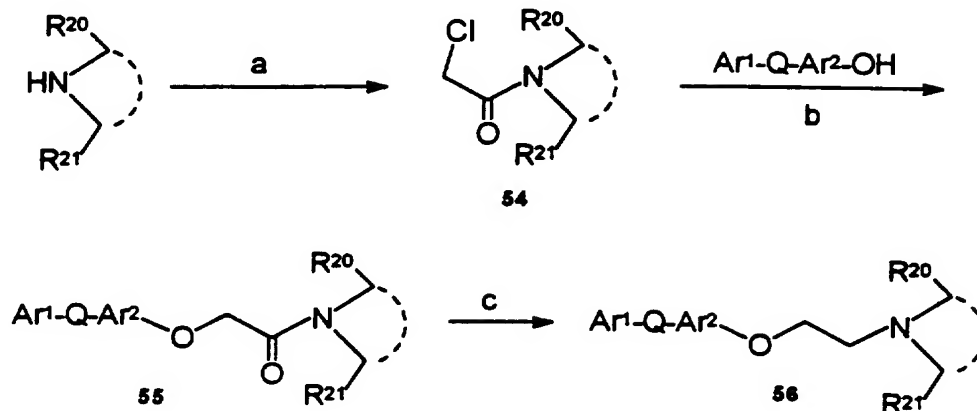
Scheme 14 describes yet another synthetic pathway utilizing t-butyl ester 49 as a starting material for the preparation of compounds of Formula I. Here, the t-butyl ester is deprotected with trifluoroacetic acid in methylene chloride to afford the corresponding acid 51 which is then coupled to an amine compound of the

formula  using DSC in pyridine and DMF to yield

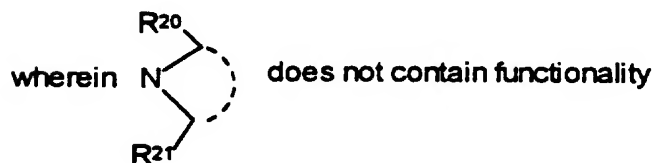
amide 52. As depicted, R^{20} and R^{21} are independently hydrogen or alkyl and optionally the defined amine may be a cyclic amine. Amide 52 may be reduced with lithium aluminum hydride in THF to give compound 53, provided that neither R^{20} nor R^{21} is (nor comprises) a functional moiety, such as an amide, ester, nitrile or the like, which is reactive toward LAH. Compound 53 is a compound of formula I.

- 55 -

Scheme 15



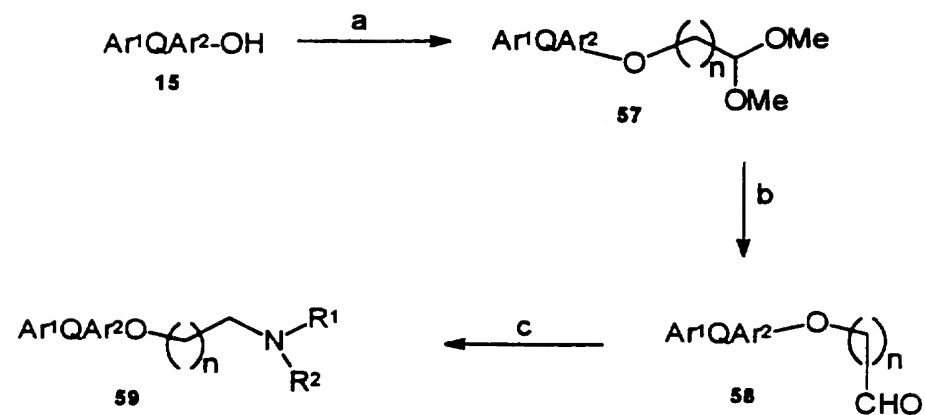
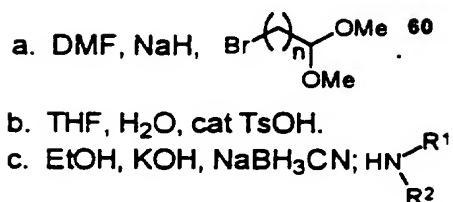
- a) Chloroacetylchloride, $\text{CH}_2\text{Cl}_2/\text{Pyridine}$, 0°C .
b) DMF, NaH.
c) LAH, THF.



reactive towards LAH reduction.

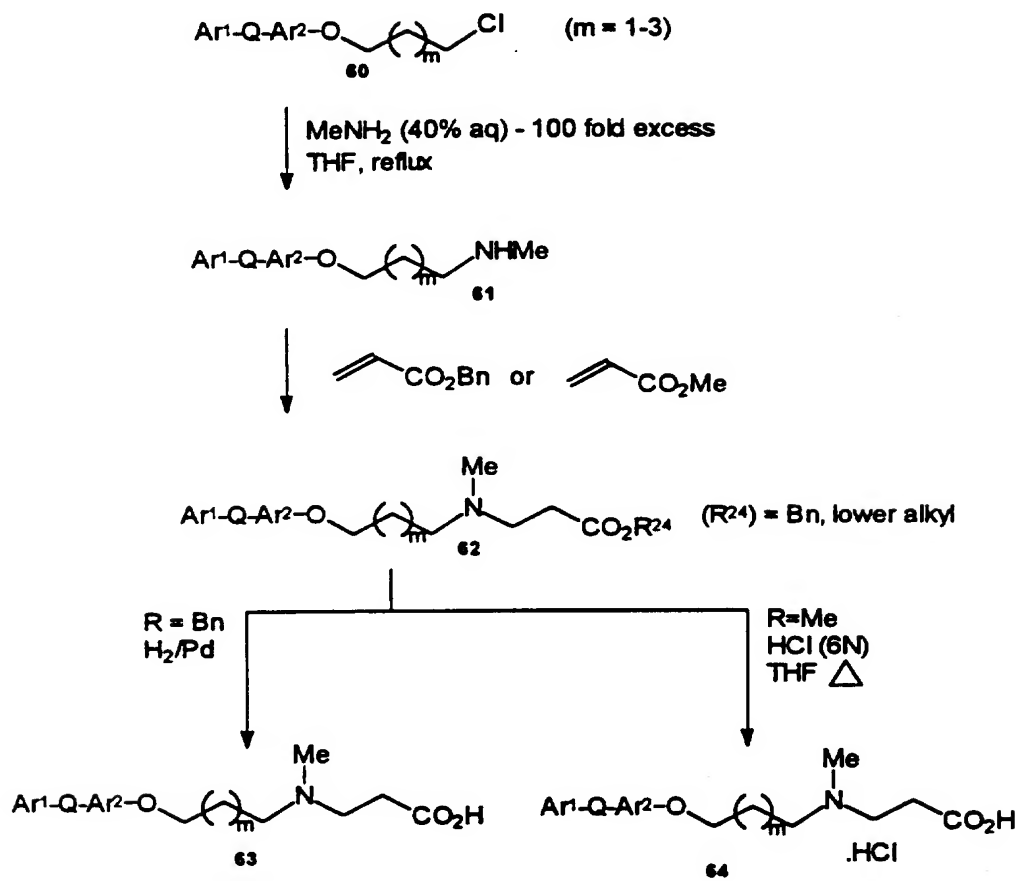
Scheme 15 depicts a preferred method for preparing compounds of Formula I which comprise sterically hindered amines such as 2,6-dimethylpiperidine, 2,5-dimethylpyrrolidine and the like. In this method, the sterically hindered amine is acylated with chloroacetylchloride in methylene chloride/pyridine at 0°C to afford α -chloroamide 54. Alkylation of a phenol of the formula $\text{Ar}^1\text{-Q-Ar}^2\text{-OH}$ with the α -chloroamide 54 [DMF, NaH] affords amide 55. Provided that the amide group of compound 55 is the only moiety which is reactive toward LAH, reduction of compound 55 with LAH in THF provides a compound 56 which is a compound of Formula I.

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Scheme 16 $n = 1-4$ 

Scheme 16 describes yet another method for preparation of compounds of Formula I in which compound 15 is alkylated with a bromodimethyl acetal (60) in DMF in the presence of NaH to afford acetal 57. Subsequent deprotection with toluene-4-sulfonic acid in THF/H₂O affords intermediate aldehyde 58 which is reductively aminated [EtOH, KOH, NaBH₃CN] with an amine of the formula HNR¹R² to afford compound 59 which is a compound of Formula I.

- 57 -

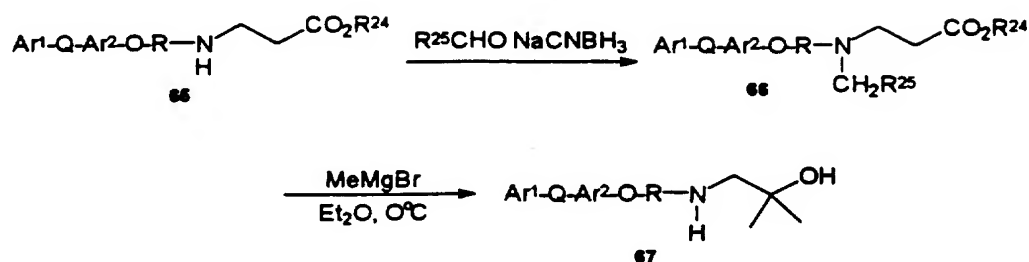
Scheme 17

- 58 -

Scheme 17 shows a preferred method for preparing compounds 63 and 64 employing an intermediate chloride 60 as an alternative to using the corresponding tosylate. Compound 60 is aminated with a 100-fold
5 excess of methylamine in acetonitrile at 60°C - 70°C to afford secondary amine 61. While compound 61 is a compound of Formula I, compound 61 may be further elaborated by reaction with a benzylacrylate ester or a methylacrylate ester to provide compound 62 which is
10 also a compound of Formula I. Where the ester 62 is a benzyl ester, it may be converted into its corresponding acid 63 by hydrogenation ($H_2/Pd/EtOH$ at 2 psi); and where ester 62 is alkyl ester, it may be converted into its corresponding acid as the
15 hydrochloride salt 64 via hydrolysis with 6N HCl in THF at 60°C.

Among the preferred compounds of the present invention are those in which the nitrogen-containing moiety (i.e., Z, as defined herein) comprises at least
20 one polar moiety, such as a carboxylic acid or ester moiety or a carboxamide, acylhydrazide, alkylamide or alanineamide moiety or the like.

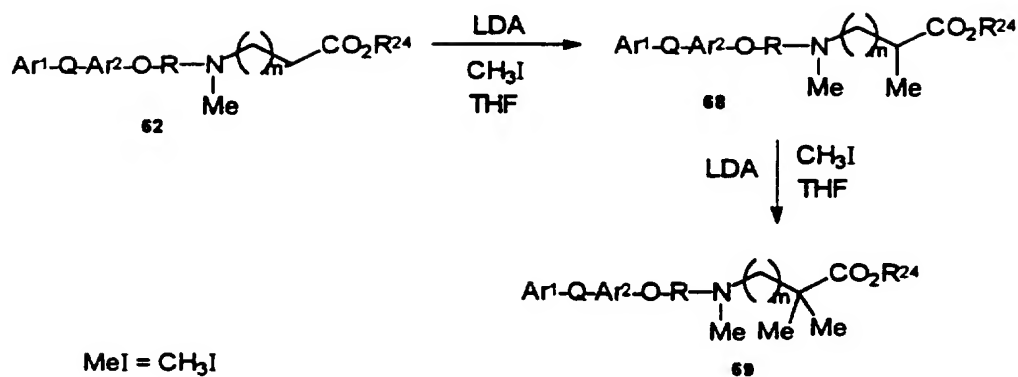
- 59 -

Scheme 18

R²⁵ = alkyl, branched alkyl, aryl.

Scheme 18 illustrates further modification of a compound 65 which is also referred to herein as a β -alanine-based compound of Formula I. Compound 65, which is representative, is reductively aminated with a C₁-C₄ aldehyde or ketone included but not limited to formaldehyde, acetaldehyde, 1-propanal, acetone, methyl-ethyl ketone and the like to provide compound 66 which is a compound of Formula I. Compound 66 may optionally be converted tertiary alcohol 67 (also a compound of Formula I) by reaction with methylmagnesium bromide in ether at 0°C.

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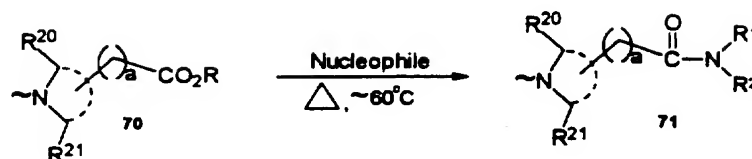
Scheme 19

- 5 Scheme 19 illustrates a method for introducing one
 or two methyl substitution(s) into the backbone of the
 β -alanine moiety of compound 62. Compound 62 may be
 sequentially alpha-methylated by reaction with LDA in
 THF at -78°C followed by quenching with methyl iodide to
 10 afford compound 68 or compound 69.

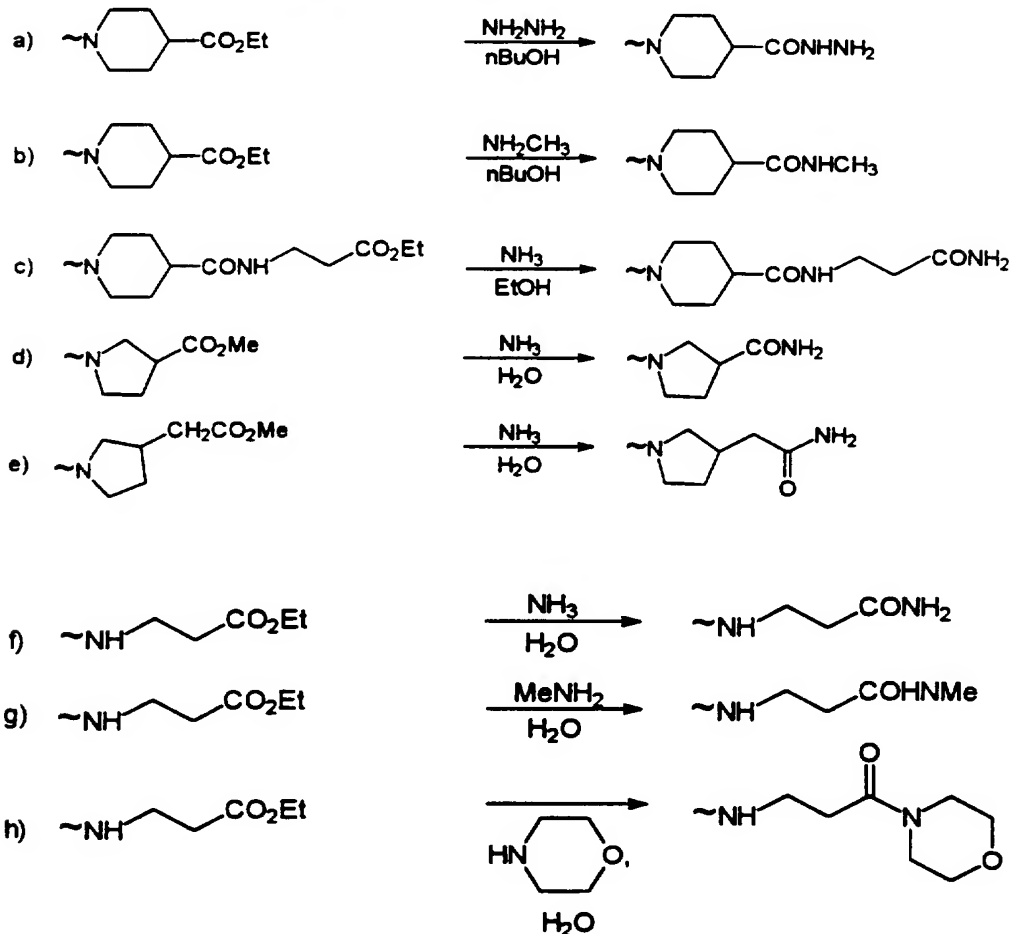
- 61 -

Schemes 20 and 21 show modification of a compound 70 comprising an ester-containing Z group to produce compound 71 or compound 72 possessing a variety of polar substitutions.

- 62 -

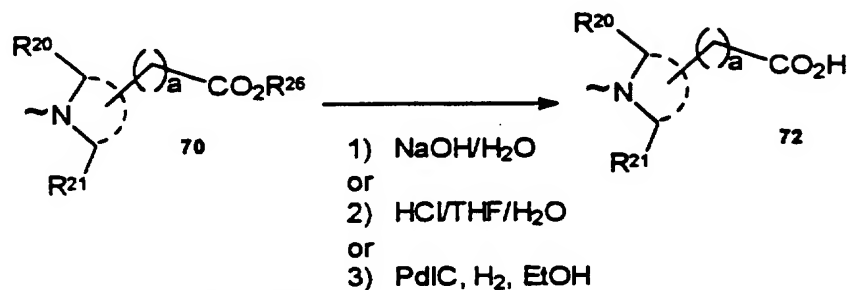
Scheme 20

where $\sim = \text{Ar}^1\text{---Q---Ar}^2\text{---Y---R---}$

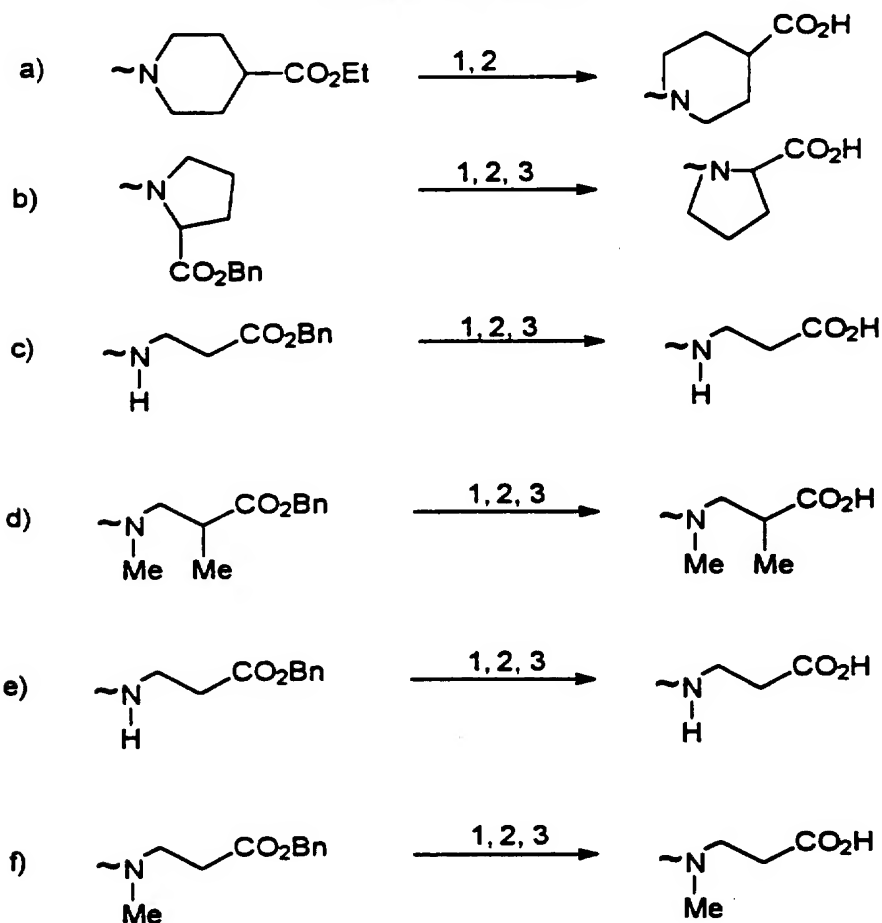
Exemplified Reactions

Scheme 20 depicts the modification of a compound 70 which comprises an ester moiety in which the ester is modified by the addition of a nucleophile such as an amine or hydrazine to provide compound 71 as shown in the "Exemplified Reactions" set forth in equations (a)-(h) of Scheme 20.

- 63 -

Scheme 21

where ~ = Ar¹-Q-Ar²-Y-R-
and R²⁶ = lower alkyl or benzyl

Exemplified Reactions

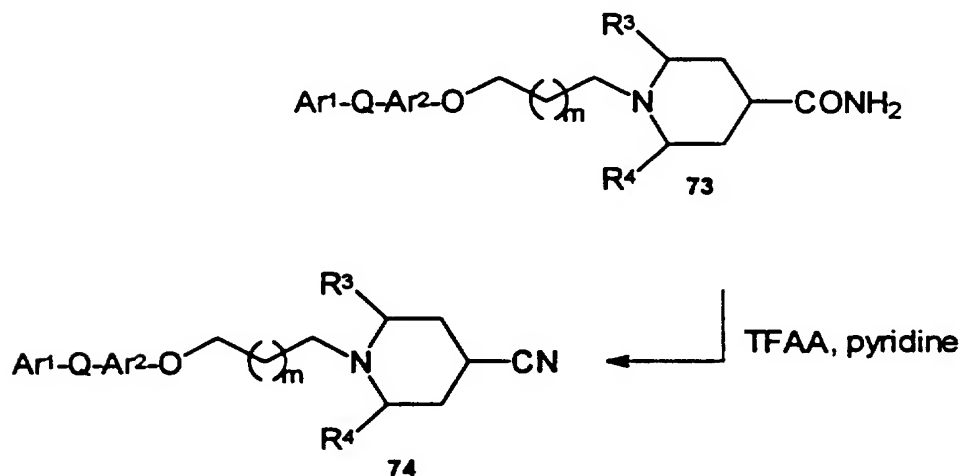
Scheme 21 shows the conversion of compound 70 which comprises an ester moiety to corresponding acid 72 via one of three reactions: (1) basic hydrolysis;
5 (2) acidic hydrolysis, which is preferred where R is a lower alkyl or benzyl; or (3) hydrogenolysis over

- 64 -

palladium on carbon in EtOH, which is especially preferred where R is benzyl.

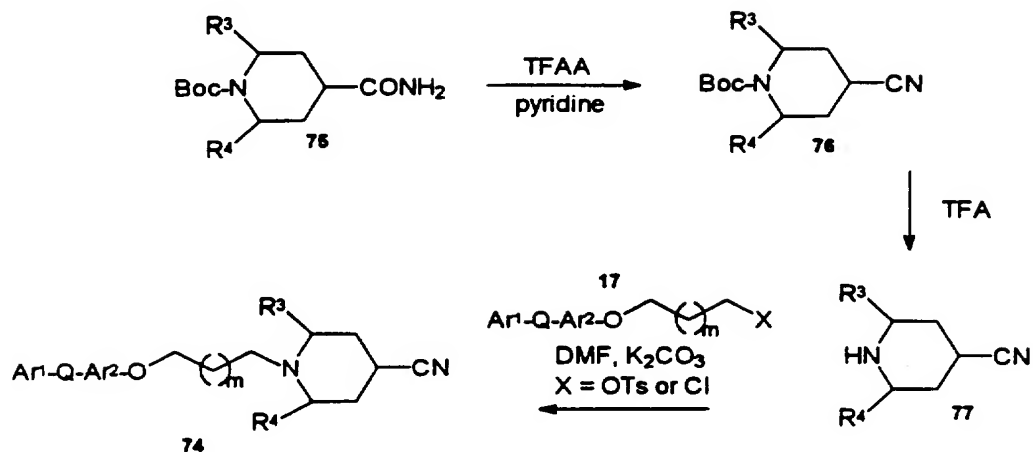
Schemes 22 and 23 show alternative methods for preparing a nitrile containing compound 74 which is a compound of Formula I and which conveniently may be employed as an intermediate in the preparation of various compounds of the present invention described in Scheme 24 below.

Scheme 22



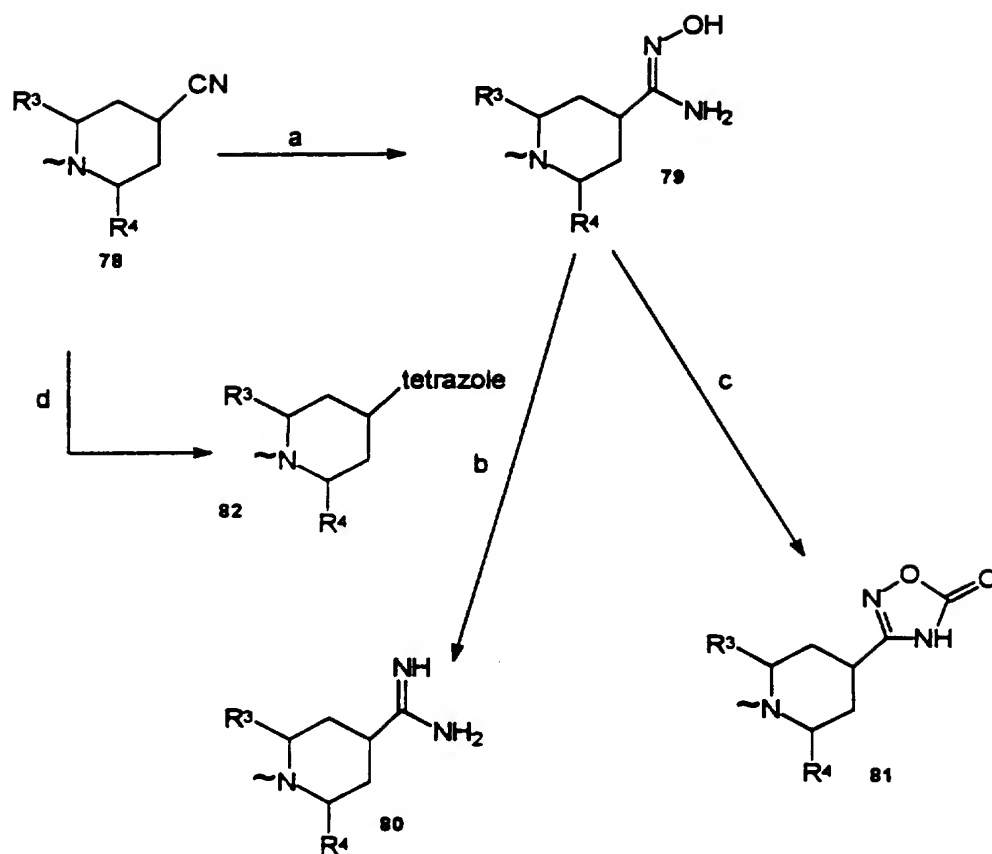
In Scheme 22 dehydration of a carboxamide containing compound 73 with trifluoroacetic anhydride in pyridine/THF at 0°C affords the corresponding nitrile containing compound 74.

- 65 -

Scheme 23

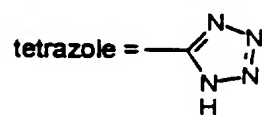
- 5 Scheme 23 shows a synthetic route to compound 74
 which is analogous to Scheme 22. In Scheme 23, the t-
 butoxycarbonyl-protected (i.e., BOC-protected)
 piperidine amide 75 is dehydrated using the conditions
 described in Scheme 22 (TFAA/pyridine) to afford
 10 protected nitrile 76. Deprotection of nitrile 76 with
 trifluoroacetic acid in methylene chloride at 0°C
 affords the corresponding secondary amine 77 which may
 be coupled to compound 17 essentially as described in
 Scheme 6 (step d) to afford nitrile-containing
 15 compounds of the present invention, which may be
 utilized as described in Scheme 24.

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Scheme 24

- a) NH₂OH
 b) H₂, 4% Pd/C, EtOH
 c) Toluene, COCl₂, 60°C
 d) Me₃SnN₃

~ = Ar¹-Q-Ar²-OR-

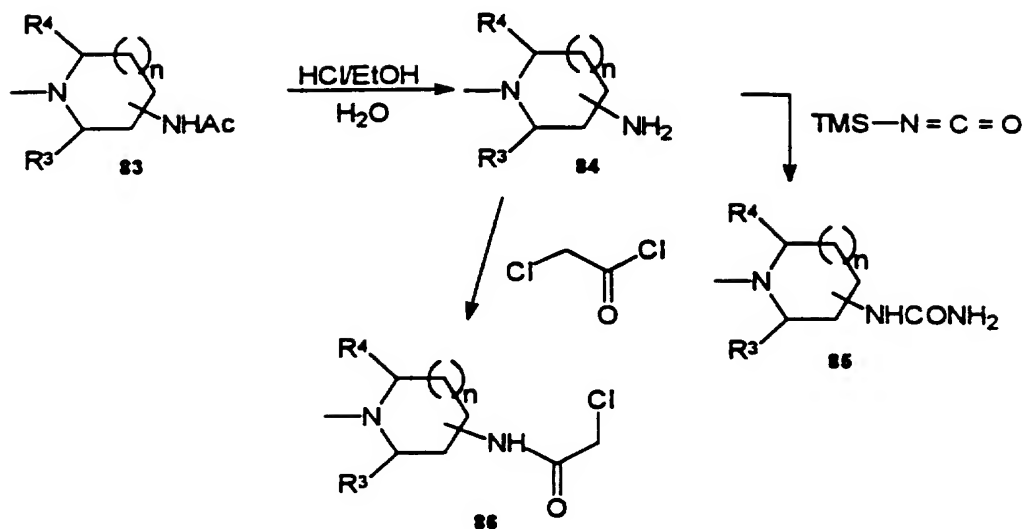


- 67 -

Scheme 24 shows several reaction pathways which may be used to modify the nitrile moiety of compound 78 to afford a variety of compounds of the present inventions. In step (a) the nitrile moiety of compound 78 is condensed with hydroxylamine in an alcoholic solvent such as ethanol, propanol, butanol, or the like to afford the corresponding hydroxyamidine 79 which is a compound of the present invention as well as an intermediate for step (b) of this Scheme. Thus, in step (b), hydroxyamidine 79 may be hydrogenated in ethanol over palladium on carbon to afford the corresponding amidine 80 which is a compound of the present invention. Alternatively, hydroxyamidine 79 may be cyclized with phosgene in toluene at 60°C to yield 81 which is a compound of the present invention. Scheme 21 furthers shows, in step d, reacting nitrile 78 with trimethyl-tin azide in xylene at 130°C to afford the corresponding tetrazole containing compound 82 which is a compound of the present invention.

20

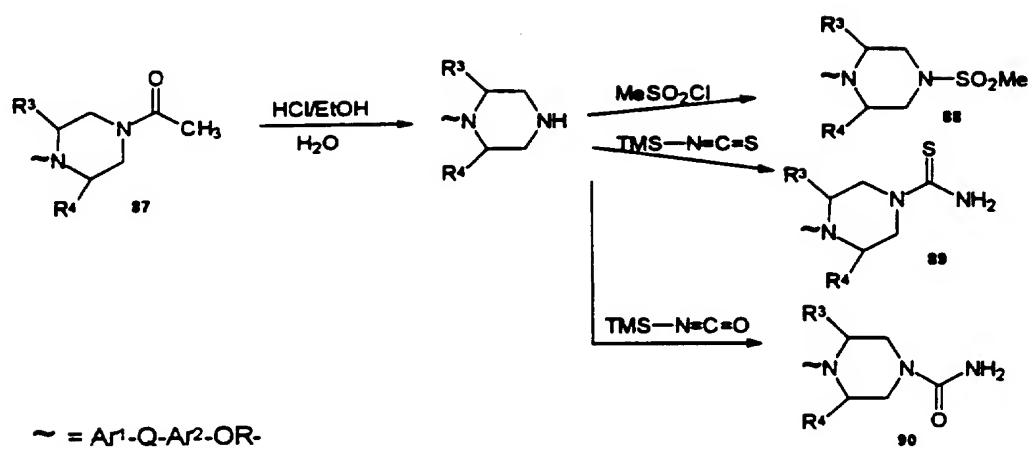
- 68 -

Scheme 25~ = Ar¹-Q-Ar²-OR-

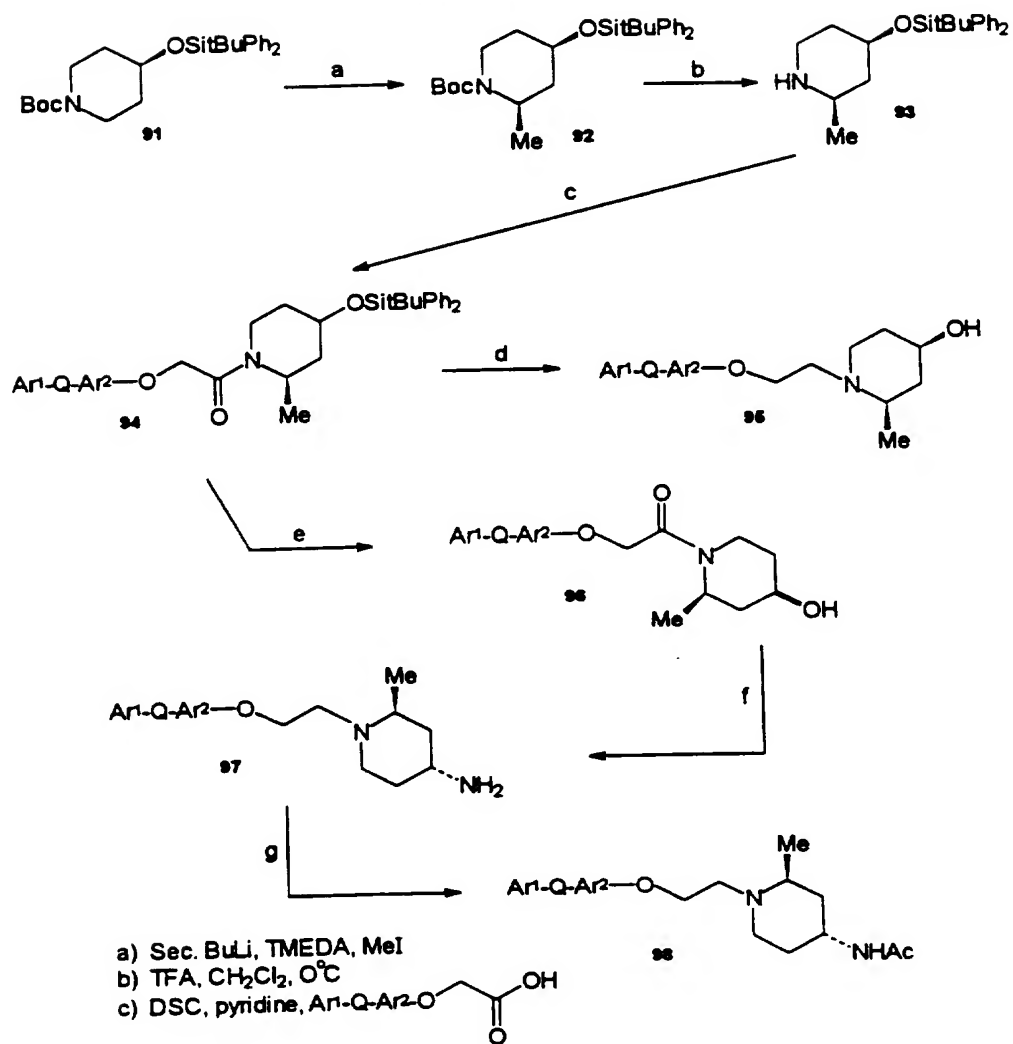
Scheme 25 illustrates modification of compounds having a cyclic amine moiety derivatized with an acetamide group (compound **83**) to convert the acetamide moiety to a primary amine ($\text{HCl/EtOH/H}_2\text{O}$ 80°-100°C) to provide compound **84** which, in turn, may be modified to a urea moiety (TMS-NCO) to provide compound **85** or to an α -chloroamide moiety to provide compound **86**. Compounds **84**, **85** and **86** are compounds of the present invention.

Compounds of the present invention containing a piperazine moiety, compound **87**, may be derivatized in essentially the same manner as described in Scheme 24 to yield derivatized piperazine compounds which include methylsulfonamide-containing compound **88**, thiourea-containing compound **89** or urea-containing compound **90**, as illustrated in Scheme 26.

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Scheme 26

- 70 -

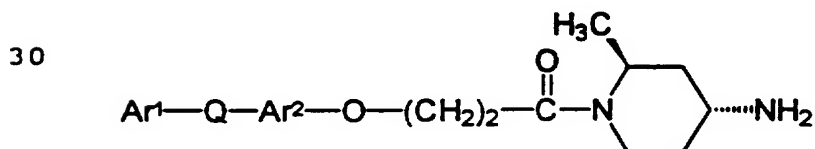
Scheme 27

- 71 -

Scheme 27 shows methods for preparing compounds of the invention having a 4-substituted 2-methyl piperadine moiety. In Scheme 27, di-protected 4-piperadol 91 is methylated in the 2-position using the method of P. Beak, et al., *J. Org. Chem.* 58, 1109 (1993). The 2-methyl derivative 92 is deprotected using trifluoroacetic acid in methylene chloride at 0°C to yield the secondary amine 93 which, in turn, is coupled to a compound of the formula $\text{Ar}^1\text{-Q-Ar}^2\text{-CH}_2\text{CO}_2\text{H}$ (compound 51, wherein R is hydrogen) using the method described in Scheme 14, step (b). The resulting amide 94 may be reduced and desilylated in one step with LAH in THF at room temperature to afford the trans di-substituted piperadine 95 which is a compound of the present invention.

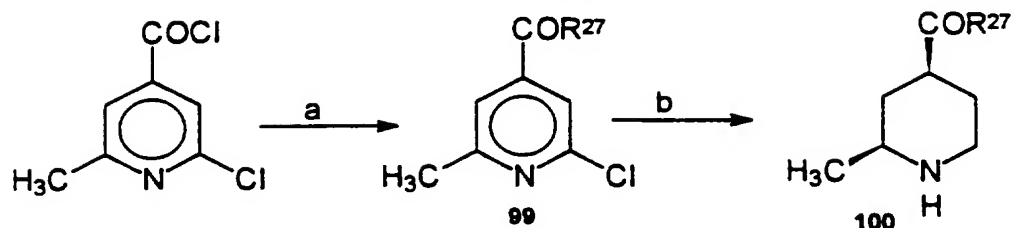
Alternatively, amide 94 may be desilylated (TBAF) to afford alcohol 96 which is subjected to a four-step reaction sequence (steps (f)(1)-(f)(4)) to afford cis 2-methyl, 4-amino piperadine 97.

The four-step reaction scheme consists of reacting the alcohol 96 with TsCl in methylene chloride/pyridine at 0°C to give the corresponding tosylate which is displaced with sodium azide in DMF (60°-80°C) to afford the corresponding azide having inverted stereochemistry (i.e., trans → cis). The azide is hydrogenated at atmospheric pressure in methanol over 4% palladium on carbon to afford the corresponding amine of the formula



the amide function of which is reduced with LAH in THF at room temperature to afford compound 97. Optional acylation of the 4-amino moiety of compound 97 affords compound 98.

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Scheme 28

a) (1) NH_4OH
 CH_2Cl_2

or
 (2) MeOH

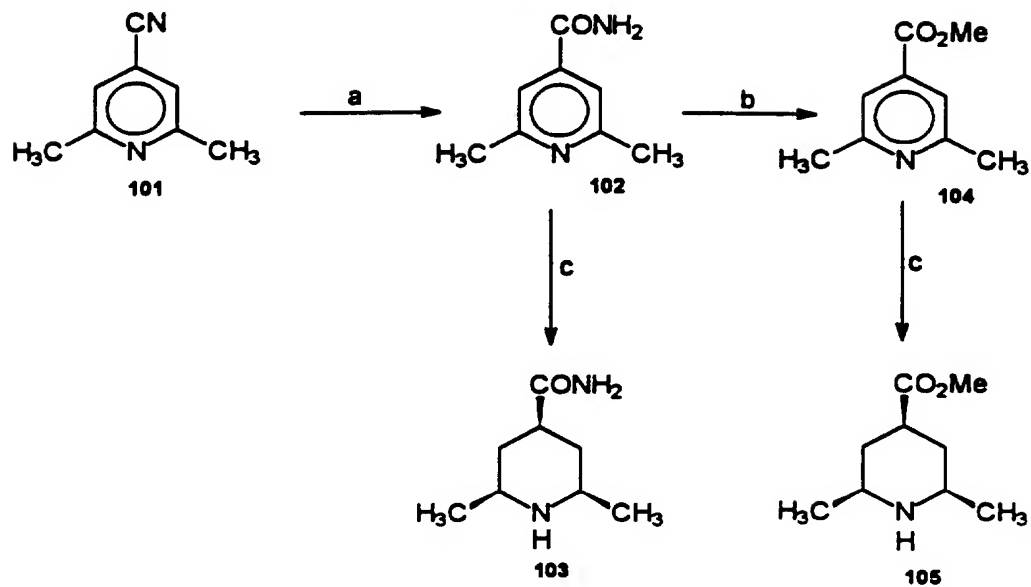
or
 (3) $\text{CH}_2\text{Cl}_2/\text{MeNH}_2$

b) H_2 , Ru, 60 psi, 140°C

$\text{R}^{27} = \text{NH}_2, \text{OCH}_3, \text{NHCH}_3$

Scheme 28 shows methods for making cis 2-methyl, 4-substituted piperidines, 100, (which are compounds encompassed within "ZH" as used herein) which compounds can be coupled in a coupling reaction as described in Scheme 6 to afford compounds of formula I. Scheme 28 starts with commercially available 2-chloro-6-methyl pyridine-4-carbonylchloride (Maybridge Chem.) which is reacted with one of the following: (1) ammonium hydroxide; (2) methanol; or (3) methylamine. The reactions each may be carried out in methylene chloride at 0°C to afford a substituted pyridine of the formula 99 wherein R is (1) NH_2 ; (2) OCH_3 ; or (3) NHCH_3 , respectively. Compound 99 is hydrogenated over ruthenium catalyst (e.g. 5% ruthenium on charcoal) at 140°C at 60 psi to afford a cis 2-methyl,4-substituted piperidine 100.

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Scheme 29a) NaOH, EtOH, H₂O₂

b) HCl (g), MeOH

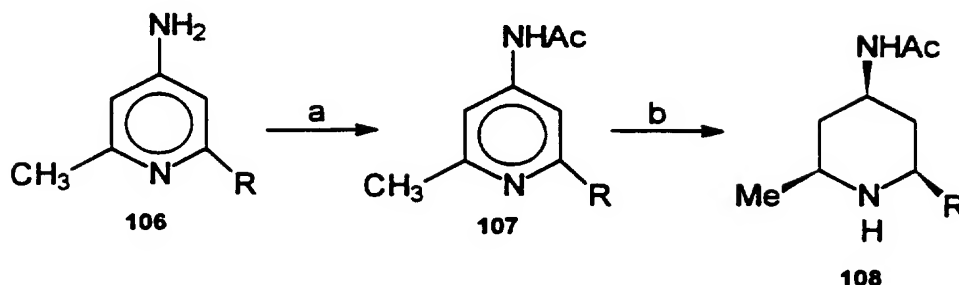
c) H₂/Ru, 60 psi, 140°C

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Scheme 29 shows methods for preparing cis 2,6 dimethyl, 4-substituted piperidines 103 and 105 (which compounds are also encompassed within "ZH" as defined herein) which may be coupled in a coupling reaction as described in Scheme 6 to afford compounds of the present invention. Scheme 29 starts from 2,6-dimethyl-4-cyanopyridine 101 which is prepared in accordance with the method of Feely, et al., JACS 81, 4004 (1959). Compound 101 is hydrolyzed using basic hydrogen peroxide in ethanol to afford primary amide 102 which, in turn, is hydrogenated under the conditions described in Scheme 28 to afford the corresponding tri-substituted piperidine 103.

Alternatively, primary amide 102 may be esterified using HCl(g) in methanol to afford the corresponding methylester 104 which, in turn, may be hydrogenated as described in Scheme 28 to afford the corresponding tri-substituted piperidine 105.

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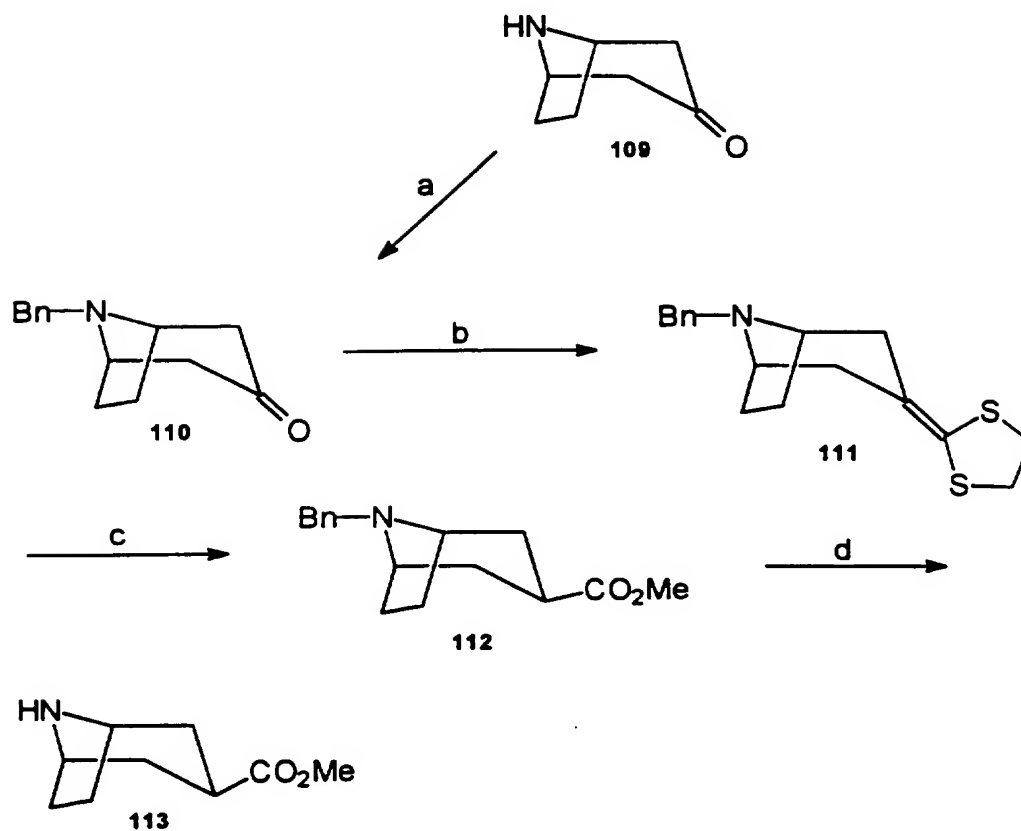
Scheme 30

R is H or Me

a) Ac₂O, pyridineb) H₂/Ru, 60 psi, methanol

Scheme 30 shows methods for preparing 2-methyl 4-substituted piperidines and 2,6-dimethyl 4-substituted piperidines 108 which can be coupled as described in Scheme 6 to afford compounds of the present invention. In Scheme 30, compound 106 may be prepared by the combination of the method of R.F. Evans et al., JOC 27, 1665 (1962), followed by the method of R.J. Martins et al., RECUEIL 86, 655 (1967). Compound 106 is acetylated using acetic anhydride and pyridine and the resultant acetamide 107 is hydrogenated under the conditions described in Scheme 28 to afford compound 108.

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Scheme 31

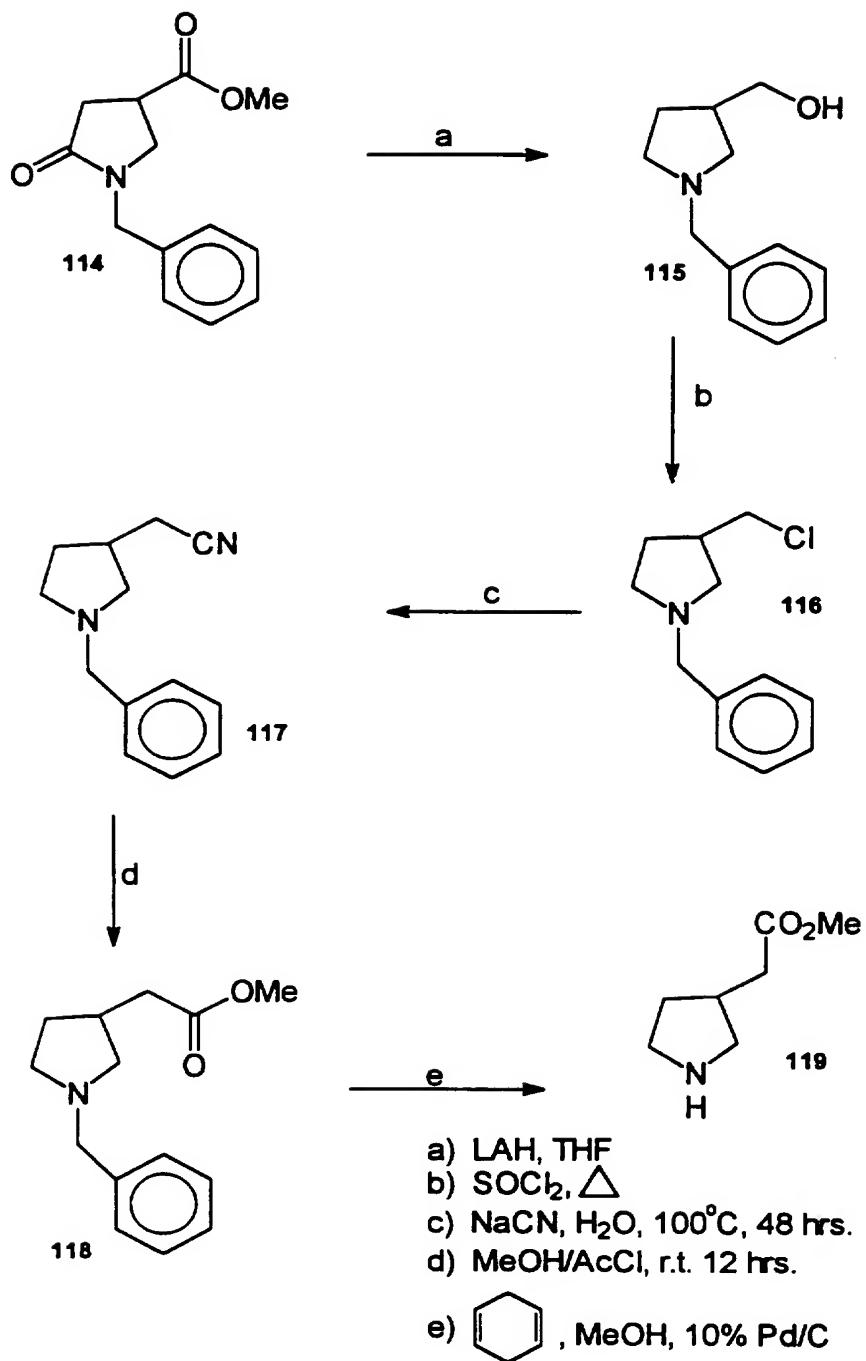
- a) DMF, K_2CO_3 , BnBr $0^\circ C \longrightarrow$ r.t.
b) Trimethylsilyldithiane, THF, nBuLi, $0^\circ C$.
c) CH_3OH , 6N HCl, $HgCl_2$, TFA.
d) CH_3OH , conc. HCl, $Pd(OH)_2/C$, 60 psi.

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Scheme 31 shows a method for preparing substituted tropones (referred to herein as "ZH") which tropones may be coupled in accordance with Scheme 6 to provide compounds of the present invention. In Scheme 28, 5 tropone 109 (which may be derived from commercially available N-methyl tropone) is N-benzylated with benzylbromide in DMF in the presence of K_2CO_3 at $0^\circ C$ to provide 110 which is homologated with the lithium anion derived from dimethylsilyldithiane (THF, $nBuLi$, 10 $0^\circ C$) to give the dithiane adduct 111.

The dithiane adduct 111 is converted into the corresponding methyl ester using mercuric chloride-catalyzed hydrolysis in methanol to provide methyl ester 112 which is debenzylated via hydrogenation in 15 methanol/concentrated hydrochloric acid over palladium hydroxide on carbon at 60 psi to afford carboxymethyl-substituted tropane 113. It should be understood that such carboxymethyl-substituted tropanes may be further modified in accordance with the method described in 20 Schemes 20 and 21 to provide a wide variety of substituted tropones.

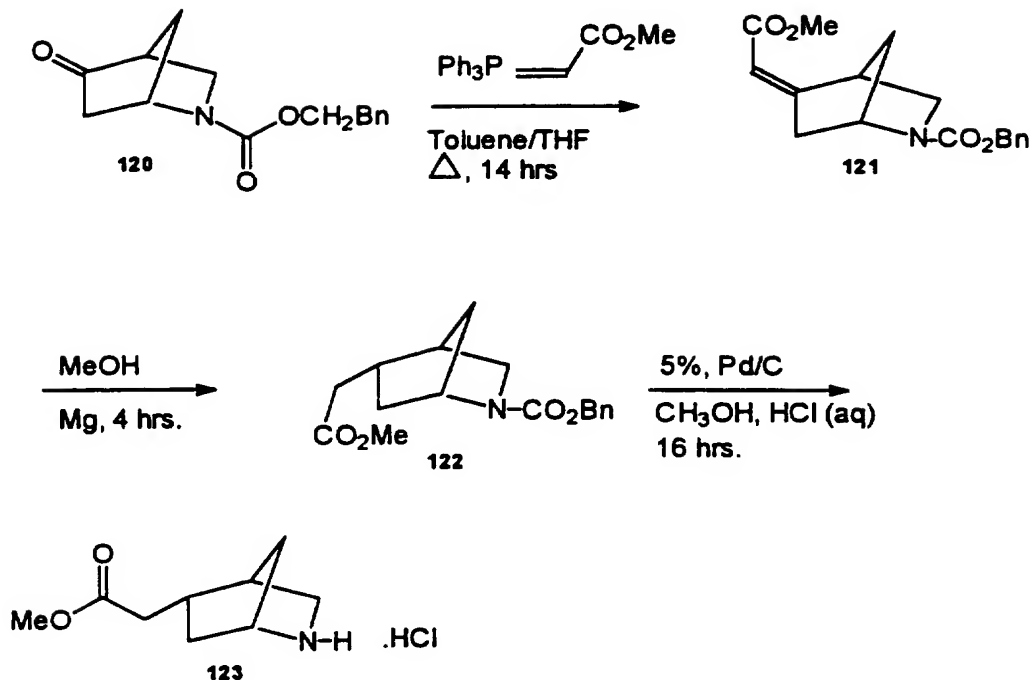
- 78 -

Scheme 32

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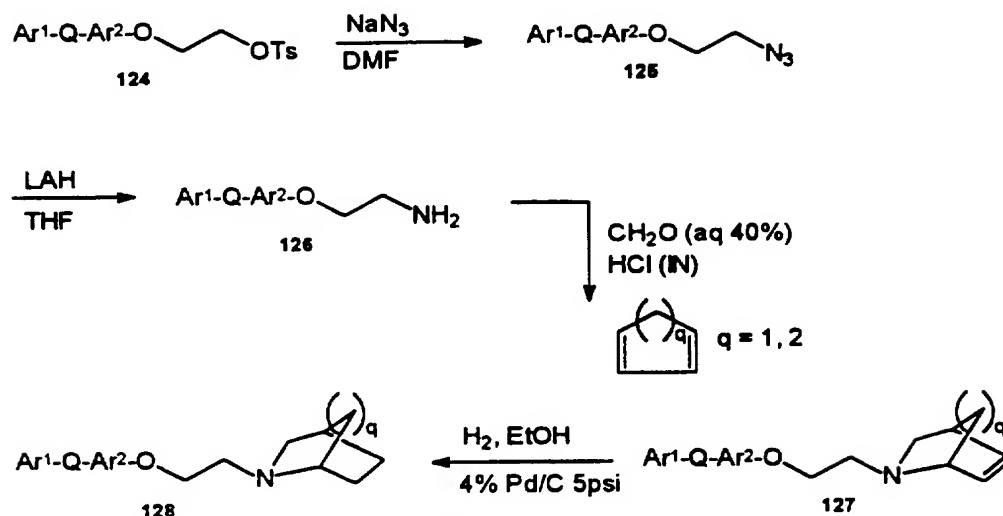
Scheme 32 shows the preparation of 3-substituted pyrrolidine 119 from methy-1-benzyl-5-oxo-3-pyrrolidine carboxylate 114 which is commercially available. In step (a) of Scheme 32 compound 114 is reduced with LAH in THF at room temperature to afford alcohol 115, which is then reacted with thionyl chloride at reflux to give to the corresponding chloride 116. Compound 116 is then treated with aqueous sodium cyanide at 100°C for about 48 hours to yield the nitrile 117. Hydrolysis of nitrile 117 in methanolic HCl affords methyl ester 118, which may be debenzylated using hydrogen-transfer hydrogenation conditions (1,4 cyclohexadiene, methanol 10% Pd/C) to provide the 3-substituted pyrrolidine 119.

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SCHEME 33

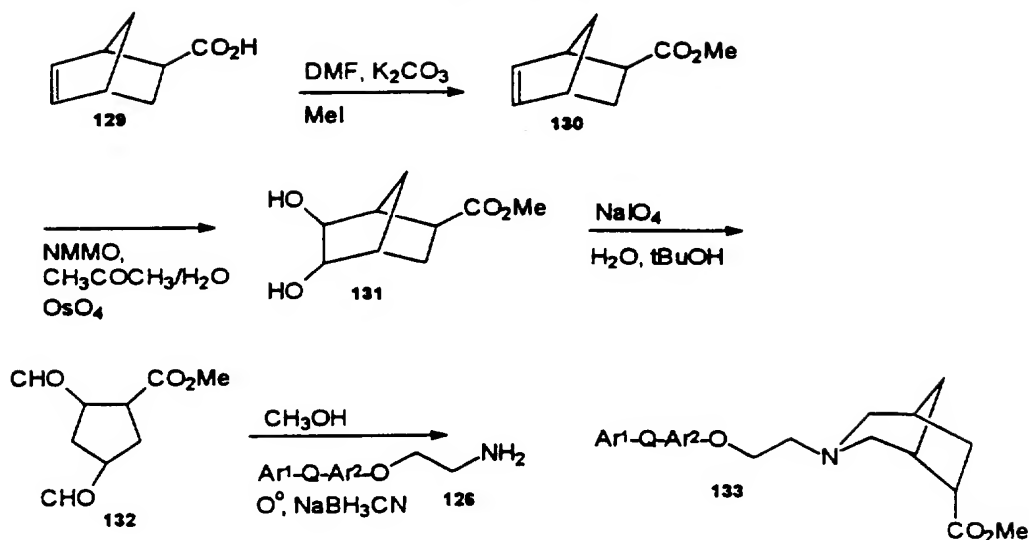
- Scheme 33 shows a 3-step procedure for the preparation of [2.2.1]-2-aza-bicycloheptane 123 from 2-(carbobenzyloxy) 2-azabicyclo[2.2.1]heptan-5-one 120. Compound 120 is prepared as described by F. Ivy Carroll, et al., J. Med. Chem. 35, 2184 (1992). Compound 120 is condensed with methyl (triphenylphosphoranylidene)acetate in THF at 50°-70°C to afford α,β unsaturated ester 121. Reduction of compound 121 with magnesium in methanol affords the corresponding saturated ester 122. Compound 122 is decarbobenzyloxylated [5% Pd/C, MeOH, aq, HCl] to afford the corresponding amine 123.

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SCHEME 34

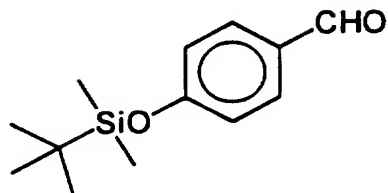
Scheme 34 shows the preparation of compounds of the present invention which are characterized as containing a 2-aza[2.2.1]bicyclo heptane or 2-aza[2.2.2]bicyclooctane moiety. Tosylate 124 is displaced with sodium azide in DMF to afford the corresponding azide 125. Azide 125 is reduced with LAH in THF to afford the corresponding primary amine 126. Primary amine 126 may be further condensed in an aza Diels-Alder reaction in the presence of either cyclopentadiene or 1,3 cyclohexadiene [40% aqueous formaldehyde, in 1N HCl] to afford azabicyclic alkenes 127 which may be hydrogenated in ethanol over 4% palladium on carbon at 5 psi to afford compounds 128. Compounds 126, 127 and 128 are compounds of the present invention.

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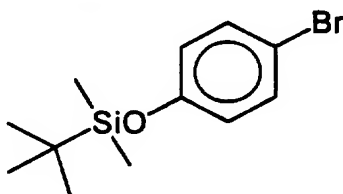
SCHEME 35

Scheme 35 describes preparation of compounds 133
 5 of the invention having a 3-aza[3.2.1]bicyclo octane-7-
 methoxycarbonyl moiety. 5-norbornene-2-carboxylate is
 esterified in DMF containing methyl iodide and
 potassium carbonate. The resulting methyl ester 130 is
 dihydroxylated with catalytic osmium tetroxide in
 10 acetone/H₂O using N-methylmorpholine oxide to recycle
 the catalyst. The resulting diol 131 is cleaved with
 aqueous sodium periodate in t-butanol to afford
 dialdehyde 132. Condensation of dialdehyde 132 with
 amine 126 in methanol followed by reduction with sodium
 15 cyanoborohydride affords compound 133 which is a
 compound of the invention.

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Example 1

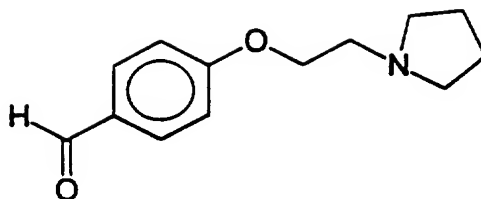
5
10 To a stirred solution of 4-hydroxybenzaldehyde (12.3 g, 0.1 mol, Aldrich) in DMF (50 mL) was added t-butyldimethylsilyl chloride (18.1 g, 0.12 mol) and imidazole (17 g, 0.25 mol). The mixture was stirred at room temperature for 16 hours, and diluted with pentane (200 mL). The organic layer was washed with water (3
15 X) and brine, dried over Na_2SO_4 and concentrated in vacuo to give 25 g of the title compound as yellow oil. The resulting product had the following properties: ^1H NMR: 300 MHz spectrum consistent with proposed structure.
20 $M^+ = 236$.

Example 2

25
30 The compound of example 2 was prepared in the same manner as described in example 1, replacing 4-hydroxybenzaldehyde by 4-bromophenol. The resulting product had the following properties: ^1H NMR: 300 MHz spectrum consistent with proposed structure. Analysis Calcd for $\text{C}_{12}\text{H}_{19}\text{OSiBr} \cdot 0.4\text{H}_2\text{O}$: C, 48.94; H, 6.78. Found: C, 48.82; H, 6.73.
35 $M^+ = 287$.

Example 3

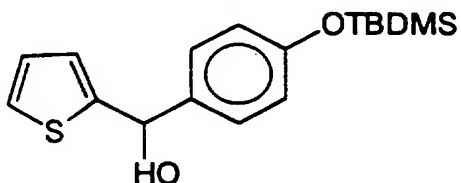
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5 The
title

compound was prepared in the same manner as Example 44
sustituting 4-hydroxybenzaldehyde. The crude aldehyde
was chromatographed (silica gel, methanol/methylene
10 chloride/ammonium hydroxide 5/94/1) to afford an amber
oil. The product had the following properties:
H.R.M.S. M^+ calcd for $C_{13}H_{17}NO_2$: 219.1259. Found
219.1239.

15

Example 4

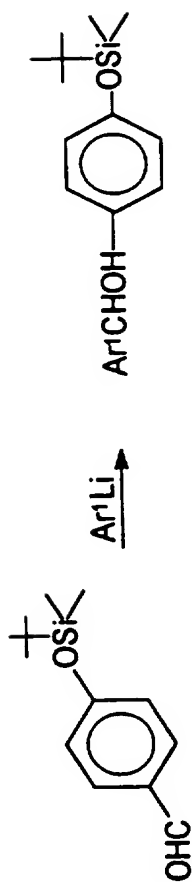
20

2-Bromothiophene (815 mg, 5 mmols, Aldrich) was
dissolved in dry THF (20 mL) and cooled to -78°C .
n-Butyllithium (3.4 mL of 1.6M solution) was added and
25 the reaction was stirred for 2 hours under Argon. The
aldehyde of Example 1 (1.18 g, 5 mmols) in THF (1 mL)
was added and reaction mixture allowed to warm to room
temperature over 1.5 hours. Water was added and the
solution was extracted with ethyl acetate (3 X 30 mL).
30 The combined organic layers were washed with brine,
dried over Na_2SO_4 , filtered and concentrated in vacuo.
The residue was chromatographed on silica gel using
EtOAc/Hep (20/80) as eluant to give 160 mg of compound
as yellow oil. The resulting product had the following
35 properties: ^1H NMR: 300 MHz spectrum consistent with
proposed structure.

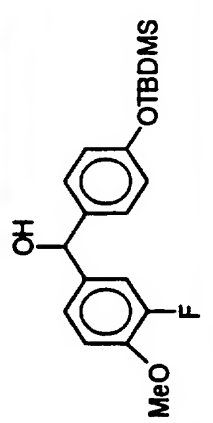
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The compounds exemplified in Table 1 were prepared essentially as described in Example 4 above except that 2-bromothiophene was replaced with the indicated aryl(halide) compound.

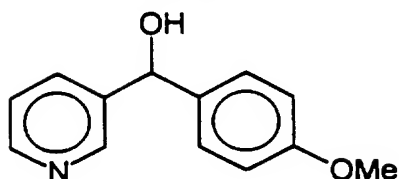
TABLE 1



Ex. No.	Compound	Aryl(halide)Ar'	Analysis
5		3-bromothiophene	$\text{C}_{17}\text{H}_{24}\text{O}_2\text{Si}$ Calc: C, 63.70; H, 7.55 Found: C, 63.85; H, 7.42
6		thiazole	$\text{C}_{16}\text{H}_{23}\text{NO}_2\text{Si}$ Calc: C, 58.78; H, 7.28; N, 4.28 Found: C, 63.85; H, 7.42; N, 4.14
7		4-bromoanisole	$\text{C}_{20}\text{H}_{28}\text{O}_3\text{Si}$ Calc: C, 69.72; H, 8.19 Found: C, 69.55; H, 8.29 M ⁺ 344.
8		Ex 2 + 3-fluorobenzaldehyde	$\text{C}_{19}\text{H}_{25}\text{FO}_2\text{Si}$ Calc: C, 68.64; H, 7.58 Found: C, 68.39; H, 7.69.

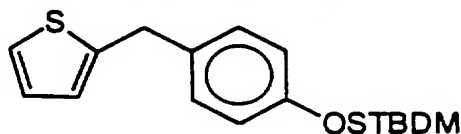
Ex. No.	Compound	Aryl(halide)Ar ¹	Analysis
9		3-fluoro-p-anisaldehyde Aryl(halide (Ar ¹))	Compound was fully characterized in the next step. See Example No. 314.

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Example 10

4-Bromoanisole (1.5 g, 8 mmol, Aldrich) was dissolved in dry THF (35 mL) and cooled to -78°C . n-Butyllithium (5 mL of 1.6M solution) was added and the reaction was stirred for 2 hours under Argon. 3-pyridinecarboxaldehyde (856 mg, 8 mmol) in THF (1 mL) was added and reaction mixture allowed to warm to room temperature over 1.5 hours. Water was added and the solution was extracted with ethyl acetate (3 X 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was chromatographed on silica gel using EtOAc/Hep (20/80) as eluant to give 1 g of compound as white solid. The resulting product had the following properties: ^1H NMR: 300 MHz spectrum consistent with proposed structure. Analysis calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_2 \cdot 0.1 \text{ H}_2\text{O}$: C, 71.94; H, 6.13; N, 6.45. Found: C, 72.04; H, 6.19; N, 6.39.

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Example 11

The product of example 4 (0.5 mmol) was mixed with Et_3SiH (0.5 mL, Aldrich) and TFA (0.4mL) and stirred at room temperature for 6 hours under Argon. The reaction mixture was concentrated and the residue obtained was basified with 10% aqueous NaOH solution. The reaction solution was extracted with ether (3 X 10 mL). The

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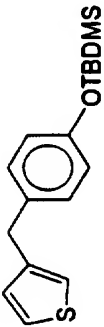
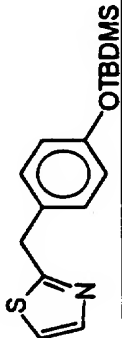
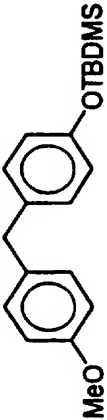
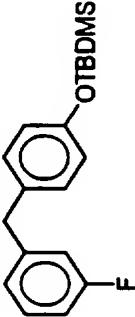
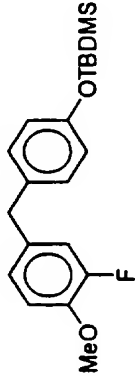
- 89 -

combined organic layers were washed with brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated to give 160 mg product. The resulting product was fully characterized in the next step. See Example No. 148.

- 5 The compounds exemplified in Table 2 were prepared essentially as described in Example 11, above, except that the precursor compounds of Examples 5-10 were substituted for the compound of Example 4.

TABLE 2



Ex. No.	Compound	Ar ¹ CH(OH)Ar ² -OR	Analysis
12		Ex. 5	Compound was fully characterized in the next step. See Example No. 149.
13		Ex. 6	C ₁₉ H ₂₃ NOSIS Calc: C, 62.90; H, 7.59; N, 4.58 Found: C, 62.60; H, 7.76; N, 4.36
14		Ex. 7	M ⁺ = 328
15		Ex. 8	Compound was fully characterized in the next step. See Example No. 22.
16		Ex. 9	Compound was fully characterized in the next step. See Example No. 314.

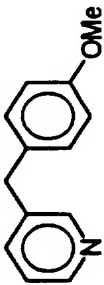
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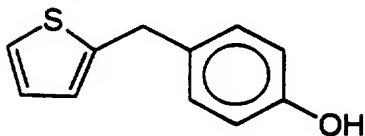
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Ex. No.	Compound	Ar ¹ CH(OH)Ar ² -OR	Analysis
17		Ex. 10	M ⁺ = 199

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Example 18

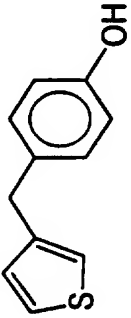
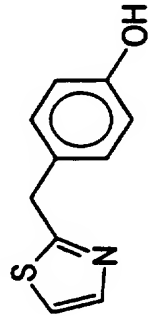
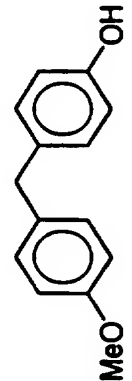
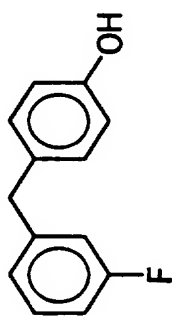
5

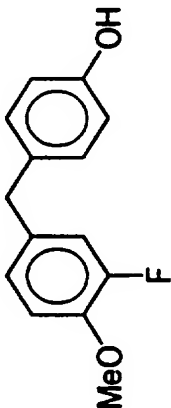
The product of example 11 was treated with tetrabutylammonium fluoride (2.5 mL of 1M solution, Aldrich) and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure, the residue obtained was treated with water and ether. The organic layer was separated and washed two times with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 90 mg of the title compound as yellow oil. The resulting product was fully characterized in the next step. See Example No. 148.

The compounds exemplified in Table 3 were prepared essentially as described in Example 18, above, except that the silylated precursor compounds indicated in Table 3 were substituted for the compound of Example 11.

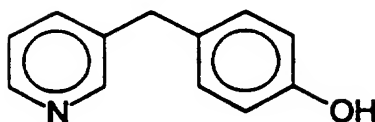
TABLE 3



Ex. No.	Compound	Ar ¹ CH ₂ Ar ² -OR	Analysis
19		Ex. 12	Compound was fully characterized in the next step. See Example No. 149.
20		Ex. 13	Compound was fully characterized in the next step. See Example No. 231.
21		Ex. 14	M ⁺ = 214
22		Ex. 15	C ₁₃ H ₁₁ OF 0.3H ₂ O Calc: C, 75.20; H, 5.63. Found: C, 75.37; H, 5.61. M ⁺ = 202

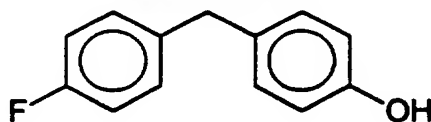
Ex. No.	Compound	$\text{Ar}^1\text{CH}_2\text{Ar}^2\text{-OR}$	Analysis
23		Ex. 16	Compound was fully characterized in the next step. See Example No. 314.

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Example 24

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The product of example 17 (500 mg, 2.5 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to -78°C . Boron tribromide (3 mL of 1M solution in CH_2Cl_2 , Aldrich) was added and the reaction mixture allowed to warm to room temperature over 1 hour. The reaction mixture was continued to stir for 6 hours. Water was added and the reaction solution was extracted with CH_2Cl_2 (30 mL X 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The resulting product had the following properties: ^1H NMR: 300 MHz spectrum consistent with proposed structure.

 $M^+ = 185$.Example 25

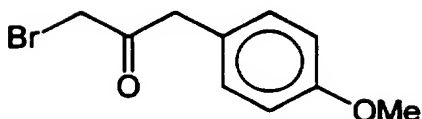
20

4-Fluoro-4'-hydroxybenzophenone (2 g, 9.3 mmol) was dissolved in EtOH (85 mL) and water (17 mL) and cooled to 0°C . Sodium borohydride (1.7g, 46 mmol) was added and the mixture was stirred at room temperature for 16 hours. The mixture was treated with 1N NaOH and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4 , and concentrated. The residue was deoxygenated in the same manner as described in example 11. The resulting product had the following properties: ^1H NMR: 300 MHz spectrum consistent with proposed structure. Analysis calcd for $\text{C}_{13}\text{H}_{11}\text{OF}$ 0.1 H_2O : C, 76.53; H, 5.53. Found: C, 76.49; H, 5.46. $M^+ = 202$.

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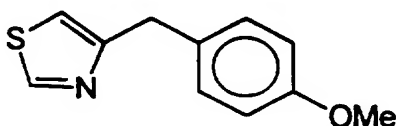
Example 26

To a solution of 4-methoxyphenylacetic acid (3.32 g, 20 mmol) in benzene (30 mL) was added oxalyl chloride (2.0 mL, 23 mmol) followed by 1 drop of DMF. The mixture was stirred at 25°C for 1.5 h and concentrated. To a solution of the crude acid chloride in ether (50 mL) at 0°C was added ethereal diazomethane until N₂ evolution ceased. HBr gas was bubbled through the solution at 0°C for 30 min (until N₂ no longer evolved). The solution was washed with water, dilute NaHCO₃, and brine and the ether layer dried over Na₂SO₄ and concentrated to provide a brown oil which was used without further purification.

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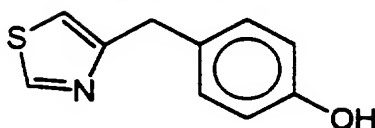
Example 27

A solution of thioformamide in dioxane was prepared by refluxing formamide (1.5 mL, 43 mmol) and P₂S₅ (3.3 g, 7.3 mmol) in 70 mL dioxane for 2 h. The solution was added to a solution of the product from Example 26 (1.0 g, 4.1 mmol) and 2 g MgCO₃ in 10 mL dioxane and the mixture refluxed for 1 h. The mixture was cooled and poured into ether and 1N NaOH. The ether layer was separated and was washed with brine, dried over Na₂SO₄ and concentrated. Flash chromatography using a gradient of 10:1 to 5:1 hexane/EtOAc provided the title compound as a colorless oil.

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Example 28

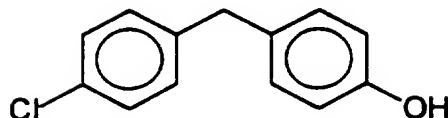
5

To a solution of the product from Example 27 (0.52 g, 2.53 mmol) in CH_2Cl_2 (10 mL) at -78°C was added 8 mL of 1N BBr_3 in CH_2Cl_2 , and the mixture stirred at -78°C for 20 min and at 25°C for 16 h. The mixture was poured into H_2O and the CH_2Cl_2 was separated, washed with brine, dried over Na_2SO_4 , and concentrated to provide the product as a boronic acid complex. The product was dissolved in methanol and treated with concentrated HCl . After stirring at 25°C for 25 h, the mixture was concentrated to give the title compound as an oil.

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Example 29

5



The compound of example 29 was prepared in the same manner as described in example 25, replacing 4-fluoro-4'-hydroxybenzophenone with 4-chloro-4'-hydroxybenzophenone. The resulting product had the following properties: ¹H NMR: 300 MHz spectrum consistent with proposed structure.

Analysis Calcd for C₁₃H₁₁OCl 0.7H₂O:

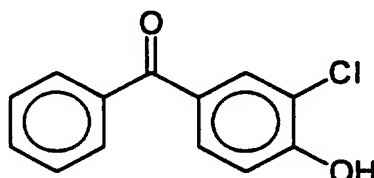
Calculated: C, 67.51; H, 5.40.

15 Found: C, 67.46; H, 5.31.

M⁺ 218.

Example 30

20



25 To a stirred solution of 2-chlorophenol (5 g, 38.9 mmol, Aldrich) and pyridine (3.2 mL, 40 mmol) in methylene chloride (100 mL) was added benzoyl chloride (0.1 mL) dropwise over 15 minutes. The solution was stirred 4 hours at room temperature and then poured
30 onto crushed ice (100 mL), allowed to warm to room temperature and stirred 18 hours. The mixture was extracted with 100 mL of ethyl acetate and the ethyl acetate was washed with 10% aqueous HCl (25 mL), water (25 mL), 10% aqueous NaOH (25 mL) water (25 mL),
35 saturated brine (25 mL) and dried over MgSO₄. After filtration, the volatile components were removed at reduced pressure on a rotary evaporator. The reaction

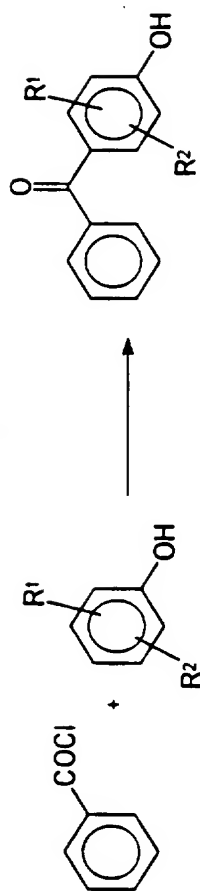
- 99 -

was assumed to be quantitative (no 2-chlorophenol present upon TLC analysis). This crude benzoate (1.1 g) without further purification was treated with aluminum chloride (1 g, 7.5 mmol) in small portions over 5 minutes. This mixture was then heated to 160°C (oil bath temperature) for 2 hours. The resulting brown mass was cooled to room temperature and treated with crushed ice/concentrated HCl (1:1 by volume, total volume 100 mL) for 30 minutes. The aqueous mixture was then extracted with two 50 mL portions of ethyl acetate. The combined extracts were washed twice with 10% aqueous NaOH (25 mL). These base extracts were combined and washed with ethyl acetate (25 mL). The base extracts were then acidified by the dropwise addition of concentrated HCl. The resulting precipitate was filtered and washed with water. This produced 0.63 g (59 %) of the title compound.

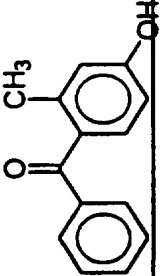
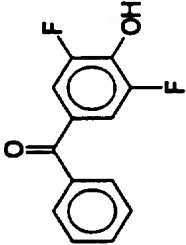
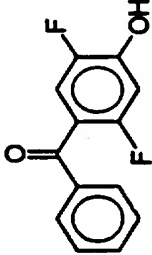
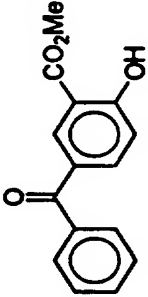
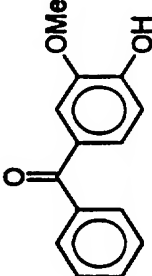
HRMS (M+) for $C_{13}H_9^{35}ClO_2$
20 Calculated: 232.0291
Found: 232.0310

The compounds exemplified in Table 4 were prepared essentially as described in Example 30 with the exception of Example 39 which was prepared from 2-methoxyphenol, benzoic acid and polyphosphoric acid at 120°C for 1 hour, with the disclosed substitutions being made for 2-chlorophenol.

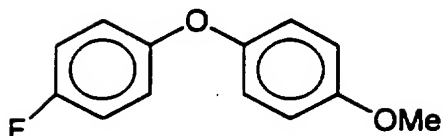
TABLE 4



Ex. No.	Compound	Ar ² OH	Analysis
31		3-chlorophenol	HRMS (M+) for C ₁₃ H ₉ ³⁵ ClO ₂ Calc: 232.0291 Found: 232.0304
32		2-fluorophenol	HRMS (M+) for C ₁₃ H ₉ FO ₂ Calc: 216.0587 Found: 216.0595
33		3-fluorophenol	HRMS (M+) for C ₁₃ H ₉ FO ₂ Calc: 216.0587 Found: 216.0588
34		2-methylphenol	Melting point Found: 173-175°C Literature: 173-174°C (J. Am. Chem. Soc., 49, 1029 (1927))

Ex. No.	Compound	Ar ² OH	Analysis
35		3-methylphenol	HRMS (MH ⁺) for C ₁₀ H ₁₀ O ₂ Calc: 213.0916 Found: 213.0913
36		2,6-difluorophenol	HRMS (M ⁺) for C ₁₃ H ₈ F ₂ O ₂ Calc: 234.0492 Found: 234.0497
37		2,5-difluorophenol	HRMS (M ⁺) for C ₁₃ H ₈ F ₂ O ₂ Calc: 234.0492 Found: 234.0494
38		2-hydroxymethylbenzoate	HRMS (M ⁺) for C ₁₆ H ₁₂ O ₄ Calc: 256.0736 Found: 256.0741
39		2-methoxyphenol	HRMS (M ⁺) for C ₁₄ H ₁₂ O ₃ Calc: 228.0786 Found: 228.0796

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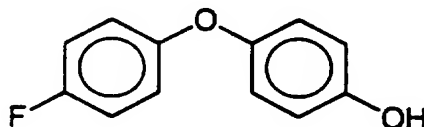
Example 40

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4-Fluorophenol (8.8 g, 78.5 mmol) and KOH (4 g, 71.3 mmol) were heated together in a round-bottom flask with a bunsen burner until the KOH dissolved. A catalytic amount of activated Cu (~100 mg) was added, followed by 4-iodoanisole (15 g, 64 mmol). The mixture was heated at 160°C for 1.75 hours and poured into cold dilute aqueous NaOH. The solution was extracted with 3 portions of ether and the combined extracts were washed with brine, dried over Na₂SO₄ and concentrated to provide the crude product. Flash chromatography on silica gel using 40:1 hexane/EtOAc gave the product (3.7 g, 17 mmol) as a colorless oil:

Anal. calc'd for C₁₃H₁₁FO₂:

Calculated: C, 71.55; H, 5.08.

Found: C, 71.44; H, 5.13.

Example 41

30
35
The product of Example 40 (1.45 g, 6.64 mmol) was stirred in 40 mL CH₂Cl₂ at -78°C and 7 mL of 1N BBr₃ in CH₂Cl₂ was added. After stirring at 0°C for 30 min and 25°C for 20 h, the mixture was poured into H₂O. The CH₂Cl₂ was separated, washed with brine, dried over Na₂SO₄ and concentrated. Recrystallization from

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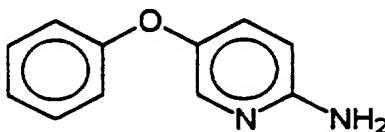
hexane/CH₂Cl₂ provided the product as a white solid: mp 91-94°C;

Anal. calc'd for C₁₂H₉FO₂·0.1 H₂O:

5 Calculated: C, 69.97; H, 4.50.
 Found: C, 69.93; H, 4.54.

Example 42

10



15

To an excess of phenol (4 g) in a round bottom flask was added K₂CO₃ (3.2 g, 23.2 mmol), CuI (110 mg, 0.58 mmol) and 2-amino-5-bromopyridine. The reaction mixture was stirred at 180°C for 16 hours, cooled to room temperature and diluted with 50 ml of 10% NaOH.

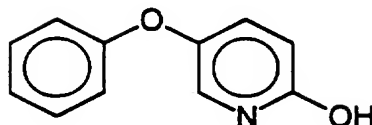
20

The aqueous layer was extracted with two 40 ml portions of ethyl acetate. The organic layers were combined, dried, concentrated and chromatographed on a 4 mm chromatotron plate (20% ethyl acetate/80% hexane). The product was identified by NMR and used in the next

25

example.

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Example 43

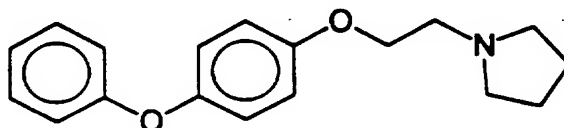
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To the product of example 42 (1.5 g, 8.1 mmol) in
20 ml of 40 N H₂SO₄ was added to NaNO₃ (685 mg, 8.1 mmol)
10 at 0° C. The reaction was then stirred at room
temperature for 0.5 hour followed by the addition of 50
ml of water. The reaction was extracted with 100 ml of
ethyl acetate, the organic layer dried and the solvent
removed *in vacuo*. Recrystallization of the crude solid
15 from 50% CH₂Cl₂/50% hexane afforded the title compound.

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Example 441-[2-(4-phenoxyphenoxy)ethyl]pyrrolidine

5



10 A solution of 4-phenoxyphenol (0.56 g, 3.0 mmol),
1-(2-chloroethyl)-pyrrolidine HCl (0.51 g, 3.0 mmol)
and powdered K_2CO_3 (1.2 g, 8.7 mmol) in 30 mL DMF was
stirred at 80-90°C for 15 hours. The solution was
cooled, poured into Et_2O and water and the ether layer
15 washed with water and brine, dried over Na_2SO_4 and
concentrated in vacuo to give 0.79 g of a brown oil.
The crude product was flashed chromatographed on silica
gel using a gradient of 2:1 hexane/EtOAc to 100 % EtOAc
to provide the title compound (0.65 g, 76.5%) as a
20 light yellow oil:

Analysis calculated for $C_{18}H_{21}NO_2$:

Calculated: C, 76.30; H, 7.47; N, 4.94.

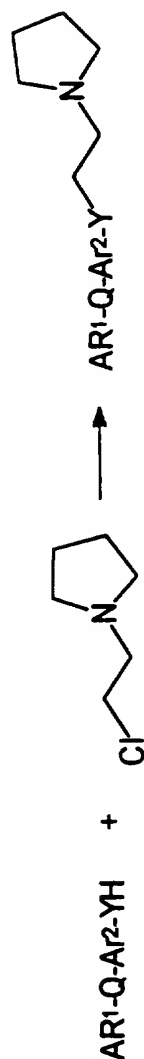
Found: C, 76.51; H, 7.50; N, 4.84.

25

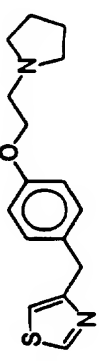
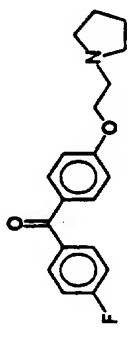
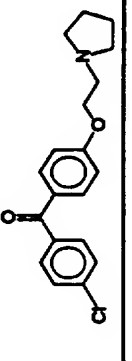
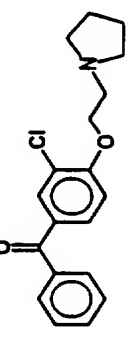
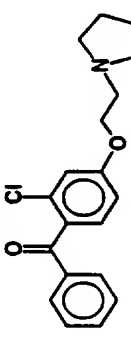
The compounds exemplified in the following Table
were prepared essentially as described in Example 44
with substitution of the indicated phenol for 4-
phenoxyphenol.

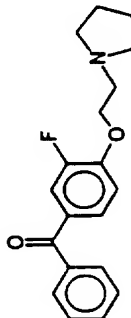
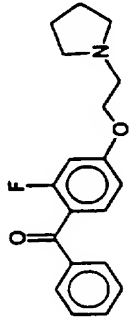
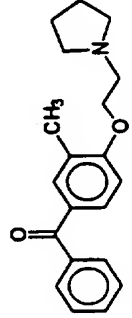
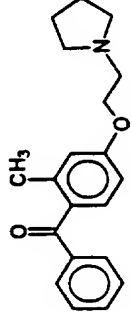
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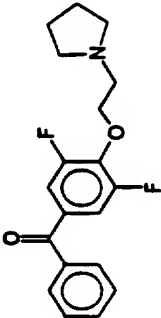
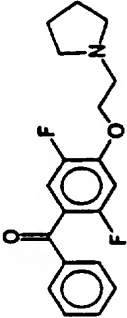
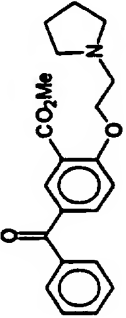
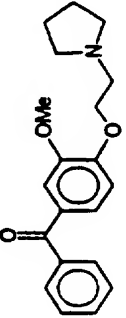
TABLE 5

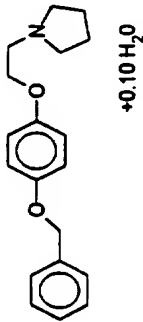
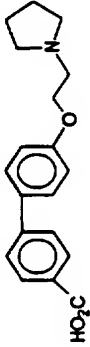
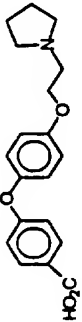
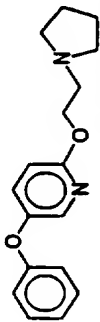


Ex. No.	Compound	Starting Material	Analysis
45		4-hydroxydiphenylmethane	$\text{C}_{19}\text{H}_{23}\text{NO}$ Calc: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.10; H, 8.36; N, 4.95.
46		trans-4-hydroxystilbene	mp 104-104.5°C; $\text{C}_{20}\text{H}_{23}\text{NO}$ Calc: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.51; H, 8.02; N, 4.70.
47		4-hydroxybenzophenone	$\text{C}_{19}\text{H}_{21}\text{NO}_2 \cdot 0.1\text{H}_2\text{O}$ Calc: C, 76.79; H, 7.19; N, 4.71. Found: C, 76.73; H, 7.12; N, 4.66.
48		Ex. 41	$\text{C}_{19}\text{H}_{20}\text{FNO}_2$ Calc: C, 71.74; H, 6.69; N, 4.65. Found: C, 71.47; H, 6.88; N, 4.47.

Ex. No.	Compound	Starting Material	Analysis
49		Ex. 28	¹ H NMR (CDCl ₃) δ 1.80 (4H, m), 2.63 (4H, m), 2.90 (2H, t), 4.08 (4H, m), 6.84 (1H, d), 6.87 (2H, d), 7.19 (2H, d), 8.66 (1H, d); HRMS, m/z 288.1286 (calc'd for C ₁₈ H ₂₀ SON ₂ , 288.1296).
50		4-fluoro-4'-hydroxybenzophenone	C ₂₄ H ₂₀ FN ₂ O ₂ : Calc: C, 72.82; H, 6.43; N, 4.47 Found: C, 72.68; H, 6.75; N, 4.35
51		4-chloro-4'-hydroxybenzophenone	C ₂₃ H ₁₉ ClN ₂ O ₂ : Calc: C, 69.19; H, 6.11; N, 4.25; Cl, 10.75 Found: C, 69.28; H, 6.10; N, 4.15; Cl, 10.49
52		Ex. 30	HRMS (M ⁺) for C ₂₃ H ₁₉ ³⁵ ClN ₂ O ₂ Calc: 329.1183 Found: 329.1186
53		Ex. 31	HRMS (MH ⁺) for C ₂₃ H ₂₁ ³⁵ ClN ₂ O ₂ Calc: 330.1261 Found: 330.1285

Ex. No.	Compound	Starting Material	Analysis
54		Ex. 32	HRMS (M+) for C ₁₁ H ₂₀ FNO ₂ Calc: 313.1478 Found: 313.1490
55		Ex. 33	HRMS (M+) for C ₁₁ H ₂₀ FNO ₂ Calc: 313.1478 Found: 313.1479
56		Ex. 34	HRMS (M+) for C ₂₀ H ₂₃ NO ₂ Calc: 309.1729 Found: 309.1707
57		Ex. 35	HRMS (M+) for C ₂₀ H ₂₃ NO ₂ Calc: 309.1729 Found: 309.1738

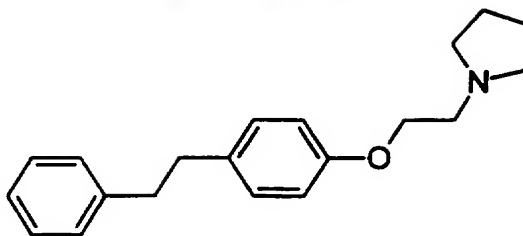
Ex. No.	Compound	Starting Material	Analysis
58		Ex. 36	HRMS (M ⁺) for C ₁₈ H ₂₀ F ₂ NO ₂ Calc: 332.1462 Found: 332.1491
59		Ex. 37	HRMS (M ⁺) for C ₁₈ H ₁₉ F ₂ NO ₂ Calc: 331.1384 Found: 331.1371
60		Ex. 38	HRMS (M ⁺) for C ₂₁ H ₂₃ NO ₄ Calc: 353.1627 Found: 353.1601
61		Ex. 39	HRMS (M ⁺) for C ₂₃ H ₂₀ NO ₃ Calc: 325.1678 Found: 325.1689

Ex. No.	Compound	Starting Material	Analysis
62	 +0.10 H ₂ O	4-[benzyloxy]phenol	C ₁₉ H ₂₃ NO ₂ · 0.10 H ₂ O: Calc: C, 76.27; H, 7.82; N, 4.68. Found: C, 76.09; H, 7.80; N, 4.62.
63	 HO ₂ C	4'-hydroxy-4-biphenylcarboxylic acid	C ₁₉ H ₂₂ NO ₃ · 1.1 H ₂ O: Calc: C, 68.90; H, 7.06; N, 4.23. Found: C, 68.87; H, 6.75; N, 3.99.
64	 HO ₂ C	4'-hydroxy-4-phenoxybenzoic acid	C ₁₉ H ₂₂ NO ₄ · 2.4 H ₂ O: Calc: C, 61.57; H, 7.02; N, 3.78. Found: C, 61.72; H, 7.10; N, 3.94. H.R.M.S. M ⁺ calcd: 328.1549. Found: 328.1550.
65		Ex. 43	C ₁₇ H ₂₀ N ₂ O ₂ · 0.1 H ₂ O: Calc: C, 71.35; H, 7.12; N, 9.79. Found: C, 71.28; H, 7.31; N, 9.51.

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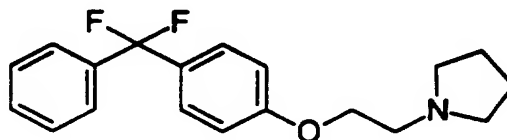
Example 66

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The product from Example 46 (0.103 g, 0.35 mmol) was hydrogenated in MeOH (20 mL) with catalytic 4% Pd/C under 5 psi H₂ pressure at 25°C for 4h. The solution was concentrated and filtered through a plug of silica gel using EtOAc to give the title compound (0.093 g, 0.315 mmol) as a colorless oil: ¹H NMR (CDCl₃) δ 1.83 (4H, m), 2.62 (4H, m), 2.87 (6H, m), 4.09 (2H, t), 6.83 (2H, d), 7.08 (2H, d), 7.19 (3H, t), 7.28 (2H, t); HRMS, m/z 295.1928 (calc'd for C₂₀H₂₅NO, 295.1936).

20

Example 67

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The product from Example 47 (0.5 g, 1.69 mmol), 1,2-ethanedithiol (0.28 mL, 3.38 mmol) and BF₃·2AcOH (0.47 mL, 3.38 mmol) were combined and stirred at 25°C for 21 h. The mixture was poured into EtOAc and aqueous NaHCO₃ and the EtOAc washed with 15% NaOH and brine, dried over Na₂SO₄ and concentrated to give the crude thioketal. A solution of 1,3-dibromo-5,5-dimethylhydantoin (0.48 g, 1.69 mmol) in CH₂Cl₂ (5 mL) was cooled to -78°C and hydrogen fluoride-pyridine (0.8 mL, 3.5 mmol) was added, followed by a solution of the thioketal in CH₂Cl₂ (3 mL). After stirring at -78°C for 1 h, the mixture was poured into CH₂Cl₂ and aqueous

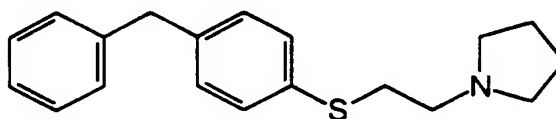
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NaHCO₃ and the CH₂Cl₂ separated, washed with brine, dried over Na₂SO₄ and concentrated to give the crude product. Flash chromatography on silica gel using a gradient of 2:1 hexane/EtOAc to 100 % EtOAc provided the title compound (0.108 g, 20%) as a light yellow oil: ¹H NMR (CDCl₃) δ 1.82 (4H, m), 2.65 (4H, m), 2.82 (2H, t), 4.15 (2H, t), 6.94 (2H, d), 7.44 (7H, m); HRMS, m/z 317.1583 (calc'd for C₁₉H₂₁NOF₂, 317.1591).

10

Example 68

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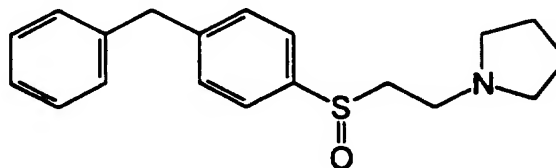
HCl

The title compound was prepared in the same manner as Example 44 using 4-benzylthiophenol as the starting material and stirring at 80°C for 6.5 h. The crude product was treated with ethanolic HCl to give, after washing with ether, the HCl salt as a white solid: mp 137-139°C; Anal. calc'd for C₁₉H₂₃NS·HCl: C, 68.34; H, 7.24; N, 4.19; Cl, 10.62. Found: C, 68.33; H, 7.27; N, 4.15; Cl, 10.36.

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Example 69

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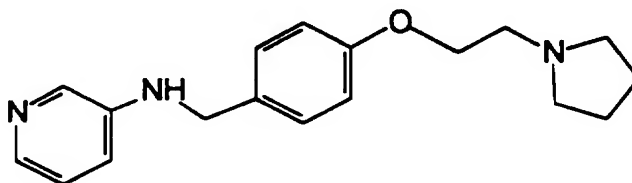
HCl

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A solution of the product from Example 68 (0.5 g, 1.5 mmol) and 80-85% mCPBA (0.32 g, ~1.5 mmol) in CH₂Cl₂

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(20 mL) was stirred at 0°C for 2 h. The mixture was concentrated and flash chromatographed on silica gel using a gradient of 100:1:1 to 100:4:1 CH₂Cl₂/MeOH/NH₄OH. The HCl salt was generated with ethanolic HCl to provide, after concentration, the title compound as a white solid: mp 180-182°C (d); Anal. calc'd for C₁₉H₂₃NOS·HCl: C, 65.22; H, 6.91; N, 4.00; Cl, 10.13. Found: C, 65.16; H, 7.20; N, 3.95; Cl, 9.84.

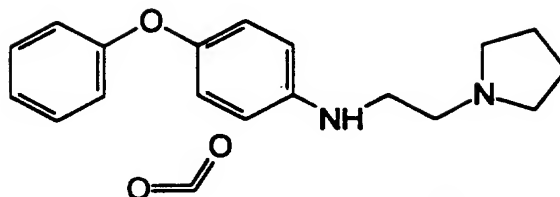
Example 70

Aminopyridine (586 mg, 6.2 mmol) was dissolved in 2 mL methanol. To the pyridine was added 2 mL 5N HCl/CH₃OH followed by the aldehyde from Example 3. Sodium cyanoborohydride (60 mg) was added to the mixture which was stirred for 12 hours at RT. The reaction was quenched with 20 mL 10% sodium hydroxide and extracted with 3 X 50 mL ethyl acetate. The combined organic phases were dried (MgSO₄), filtered and concentrated to afford a brown oil. The crude product was chromatographed (silica gel, methanol/methylene chloride/ammonium hydroxide 2/97.5//0.5) to give yellow crystals. The product had the following properties: Anal. calcd for C₁₈H₂₄N₃O·0.25 H₂O: C, 71.61; H, 7.85; N, 13.92. Found C, 71.54; H, 7.84; N, 13.78.

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Example 71

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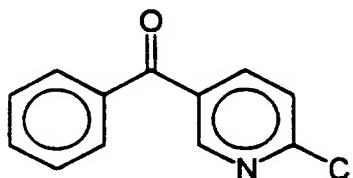
HCl

10 The title compound was prepared in the same manner as Example 44 using 4-phenoxyaniline as the starting material and stirring at 60°C for 20 h, to provide a tan solid. This was dissolved in MeOH and treated with ethanolic HCl to provide, after
15 concentration, the HCl salt. Recrystallization afforded a CO₂ complex of the product as white plates: mp 202-202.5°C; Anal. calc'd for C₁₈H₂₂N₂O·HCl·CO₂: C, 62.89; H, 6.39; N, 7.72; Cl, 9.77. Found: C, 62.64; H, 6.43; N, 7.59; Cl, 9.81.

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Example 72

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 Oxalyl chloride (0.56 ml, 6.35 mmol) was added to a stirred solution of 6-Chloronicotinic acid (1 g, 6.35
30 mmol; Aldrich) in THF (10 ml). After the addition of a drop of DMF to initiate the reaction, the mixture was stirred at room temperature for another 10 minutes. The solvent was removed in vacuo and the acid chloride was then dissolved in benzene (20 ml). AlCl₃ (2.1 g,
35 15.9 mmol) was then added slowly and the reaction was stirred at reflux for 1.5 hours. The mixture was then concentrated and flash chromatographed through a pad of

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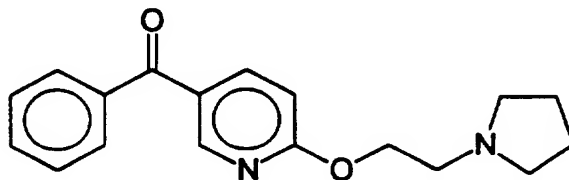
silica gel (10% EA\90% hexane) to afford 1.35 g. of a pale yellow solid. The resulting product had the following properties:

5 Analysis calculated for $C_{12}H_8NOCl$:

Calculated: C, 66.22; H, 3.70; N, 6.44.

Found: C, 66.11; H, 3.63; N, 6.32. m.p. 55°-56°C.

Example 73



NaH (75 mg, 1.84 mmol; 60% dispersion) was added to a solution of pyrrolidinoethanol (450 mg, 1.84 mmol; Aldrich) in benzene (20 ml). The mixture was stirred at room temperature for 10 minutes and then the product from example 71 was added and the reaction was allowed to stir for 4 hours. The reaction was diluted with 50 ml of EA and the organic layer was washed with 100 ml of H₂O. The organic layer was dried, concentrated, and chromatographed on a 2 mm chromatotron plate (90 CH₂Cl₂\4 MeOH\1 NH₄OH) to afford 480 mg of pure product.

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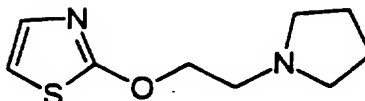
Analysis Calculated for $C_{18}H_{20}N_2O_2 \cdot 0.2 H_2O$:

Calculated: C, 72.07; H, 6.85; N, 9.34.

30 Found: C, 72.09; H, 6.89; N, 9.30.

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Example 74

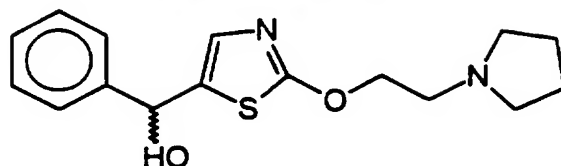


5

1-(2-hydroxyethyl)pyrrolidine (10 mL, 85.5 mmol, Aldrich) was treated with sodium hydride (50% dispersion in mineral oil, 0.5 g, 10.4 mmol) in small portions over 15 minutes and stirred 0.5 hour. To this solution was added 2-bromothiazole (1.6 g, 9.6 mmol, Aldrich) and the mixture was stirred 18 hours at room temperature. The mixture was poured into water (250 mL) and extracted with two 50 mL portions of ethyl acetate. The combined ethyl acetate extracts were washed with water (2 x 50 mL), saturated brine (50 mL) and dried over $MgSO_4$. After filtration, the volatile components were removed at reduced pressure on a rotary evaporator. The residue was chromatographed on silica gel gradient eluting with ether:hexane (1:1 to 100% ether) saturated with aqueous concentrated ammonium hydroxide. This produced 1.4 g (74 %) of the title compound.

25 HRMS (MH+) for C₉H₁₅N₂OS calculated: 199.0905
found: 199.0924

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Example 75

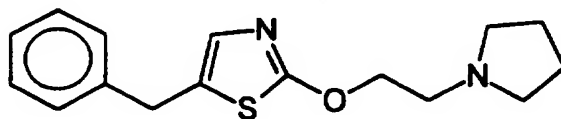
5

To a cooled (-40 °C) and stirred solution of the product of Example 74 (0.1 g, 0.5 mmol) in tetrahydrofuran (5 mL) was added n-butyllithium (1.6 M in THF, 0.38 mL, 0.6 mmol) dropwise over one minute. The mixture was allowed to warm to 0°C and stirred for 1 hour. The mixture was then treated with benzaldehyde (0.1 mL, 1.0 mmol) and stirred for 15 minutes. The mixture was poured into water (25 mL) and extracted with 25 mL of ethyl acetate. The ethyl acetate was washed 2 times with water (2 x 10 mL), saturated brine (10 mL) and dried over MgSO₄. After filtration, the volatile components were removed at reduced pressure on a rotary evaporator. This produced 0.1 g (66 %) of the title compound.

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HRMS (MH⁺) for C₁₈H₂₁N₂O₂S calculated: 305.1324
found: 305.1326

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Example 76

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The product from Example 75 (0.1 g, 0.33 mmol) was subjected to the reaction conditions described for the preparation of Example 11. The crude product was chromatographed on silica gel eluting with ethyl acetate:hexane (1:1) saturated with aqueous

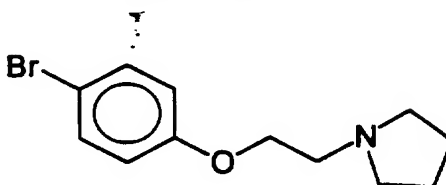
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concentrated ammonium hydroxide. This produced 0.07 g (74 %) of the title compound.

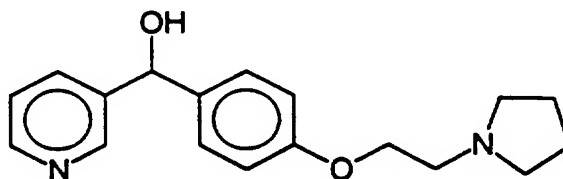
HRMS (MH+) for $C_{16}H_{21}N_2OS$ calculated: 289.1375
found: 289.1373

Example 77



A mixture of 4-Bromophenol (20g), K_2CO_3 (35g), 1°(2-Chloroethyl)pyrrolidine •HCl (19.7g) in DMF was heated to 70°C overnight. The mixture was cooled to room temperature and quenched with water, extracted with ethyl acetate. The organic phase was washed with water (3 times), dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel using EtOH/ CH_2Cl_2 / NH_4OH (4/95/1) as eluent to give 15g of title product.

Example 78



1-[2-(4-Bromophenoxy)ethyl]pyrrolidine (540.3 mg, 2 mmol, Aldrich) was dissolved in dry THF (6 mL) and cooled to -78° C. *t*-Butyllithium (2.4 mL of 1.8M solution) was added and the reaction was stirred for 4 h under Argon. 3-Pyridinecarboxaldehyde (214.2 mg, 2 mmol, Aldrich) in THF (0.5 mL) was added and reaction

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mixture allowed to warm to r.t. over 1 h. Water was added and the reaction solution was extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was chromatographed on silica gel using $\text{CHCl}_3/\text{EtOH}/\text{NH}_4\text{OH}$ (95/5/0.5) as eluant to give 220 mg of compound as yellow oil: ^1H NMR: 300 MHz spectrum consistent with proposed structure. Analysis Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2 \cdot 0.6\text{H}_2\text{O}$: C, 69.92; H, 7.56; N, 9.06. Found: c, 69.60; H, 7.31; N, 8.94.

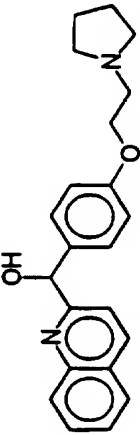
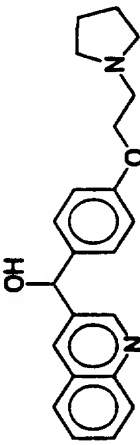
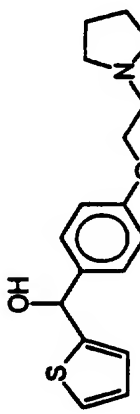
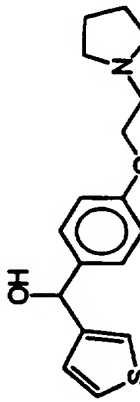
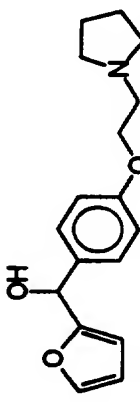
The compounds exemplified in the following Table were prepared essentially as described in Example 78.

TABLE 6

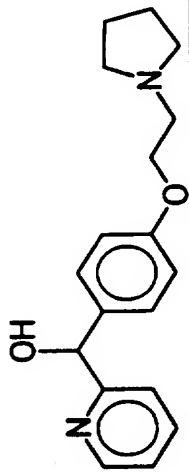
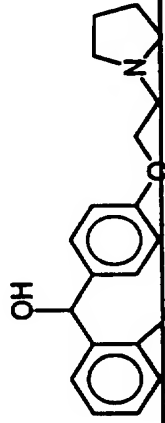
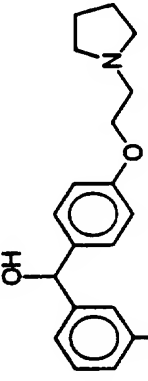
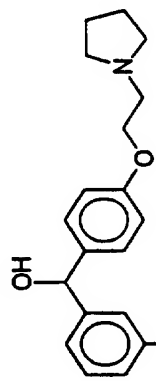


M = Li, MgBr

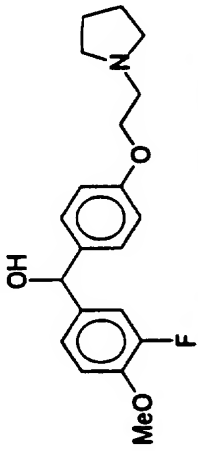
Ex. No.	Compound	Ar ¹ Precursor	Analysis
79		4-pyridinecarboxaldehyde	C ₁₈ H ₂₂ N ₂ O ₂ ·0.2H ₂ O: Calc: C, 71.59; H, 7.48; N, 9.28. Found: C, 71.63; H, 7.40; N, 9.22.
80		3-anisaldehyde	C ₂₀ H ₂₆ NO ₃ ·0.4H ₂ O: Calc: C, 71.79; H, 7.77; N, 4.19. Found: C, 71.64; H, 7.59; N, 4.19. M ⁺ = 327.
81		4-anisaldehyde	C ₂₀ H ₂₆ NO ₃ ·0.2H ₂ O: Calc: C, 72.57; H, 7.73; N, 4.23. Found: C, 72.47; H, 7.70; N, 4.51. M ⁺ = 327.
82		2-anisaldehyde	C ₂₀ H ₂₆ NO ₃ ·0.8H ₂ O: Calc: C, 70.27; H, 7.84; N, 4.10. Found: C, 70.25; H, 7.72; N, 3.73. M ⁺ = 327.

Ex. No.	Compound	Ar ¹ Precursor	Analysis
83		2-quinolinecarboxaldehyde	$C_{22}H_{21}N_2O_2 \cdot 0.4H_2O$ Calc: C, 74.30; H, 7.03; N, 7.80. Found: C, 74.23; H, 7.47; N, 7.69. $M^+ = 348$.
84		3-quinolinecarboxaldehyde	$C_{22}H_{21}N_2O_2 \cdot 0.3H_2O$ Calc: C, 74.68; H, 7.01; N, 7.92. Found: C, 74.68; H, 7.08; N, 7.81.
85		2-thiophenecarboxaldehyde	$C_{17}H_{17}NOS_2$ Calc: C, 67.29; H, 6.98; N, 4.62. Found: C, 67.14; H, 6.92; N, 4.56.
86		3-thiophenecarboxaldehyde	$C_{17}H_{17}NO_2S \cdot 1.2H_2O$ Calc: C, 62.82; H, 7.26; N, 4.31. Found: C, 62.81; H, 6.81; N, 4.36. $M^+ = 303$.
87		2-furaldehyde	$C_{17}H_{17}NO_2 \cdot 0.2H_2O$ Calc: C, 70.18; H, 7.41; N, 4.81. Found: C, 69.99; H, 7.19; N, 4.77. $M^+ = 287$.

Ex. No.	Compound	Ar' Precursor	Analysis
88		3-furaldehyde	C ₁₇ H ₂₁ NO ₃ ·0.3H ₂ O: Calc: C, 69.74; H, 7.44 N, 4.78. Found: C, 69.68; H, 7.13; N, 4.79. M ⁺ = 287.
89		piperonal	C ₂₀ H ₂₃ NO ₄ ·0.2H ₂ O: Calc: C, 69.63; H, 6.84; N, 4.06. Found: C, 69.75; H, 6.88; N, 4.09. M ⁺ = 341
90			NMR spectrum consistent with proposed structure.
91*			C ₁₉ H ₂₂ FN O ₂ ·0.1 H ₂ O, Calc: C, 71.95; H, 7.05; N, 4.41. Found: C, 71.78; H, 7.19; N, 4.43.

Ex. No.	Compound	Ar' Precursor	Analysis
92		2-pyridinecarboxaldehyde	Fully characterized in example 138.
93		2-fluorobenzaldehyde	$C_{19}H_{22}FNO_2 \cdot 0.1 H_2O$ Calc: C, 71.95; H, 7.05; N, 4.41 Found: C, 71.78; H, 7.19; N, 4.43
94		3-fluorobenzaldehyde	Fully characterized in example 142.
95		3-chlorobenzaldehyde	Fully characterized in example 143.

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Ex. No.	Compound	Ar' Precursor	Analysis
96		3-fluoro-p-anisaldehyde	Compound was fully characterized in the next step. See Example No. 144.

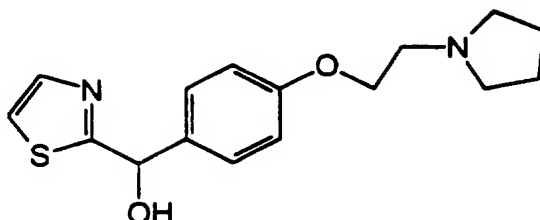
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* Compound of Example 91 was desilylated using the method described in Example 18

10

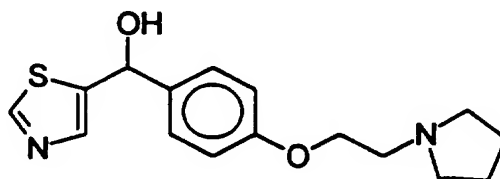
- 125 -

Example 97



To a solution of thiazole (0.5 g, 5.87 mmol) in THF (15 mL) at 0°C was added 1.6 M nBuLi in hexanes (3.75 mL, 6 mmol) and the mixture stirred at 0°C for 15 min. This solution was added to a solution of the product from Example 3 (1.1 g, 5.0 mmol) in THF (20 mL) at -78°C and the mixture stirred for 45 min. The reaction mixture was quenched with saturated NH₄Cl and poured into ether and water. The ether layer was separated, washed with brine, dried over Na₂SO₄ and concentrated. Flash chromatography on silica gel using a gradient of 100:1:0.5 to 100:2:0.5 CH₂Cl₂/MeOH/NH₄OH gave the title compound (1.12 g, 74%) as a light brown solid: Anal. calc'd for C₁₆H₂₀N₂O₂S·0.30 H₂O: C, 62.03; H, 6.70; N, 9.04. Found: C, 62.04; H, 6.64; N, 9.07.

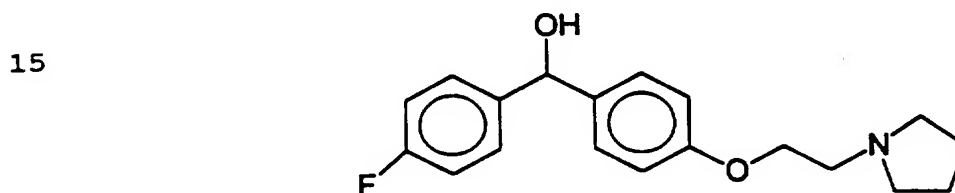
Example 98



To a solution of 2-trimethylsilylthiazole (1.09 g, 6.9 mmol) in THF (25 mL) at -78°C was added 1.6 M n-

- 126 -

BuLi in hexanes (4.5 mL, 7.2 mmol) and the mixture warmed to -50°C for 1 min and cooled to -78°C. A solution of the product from Example 3 (1.4 g, 6.4 mmol) in THF (6 mL) was added and the mixture stirred at -78°C for 45 min. The reaction mixture was quenched with saturated NH₄Cl and poured into ether and water. The ether layer was separated, washed with brine, dried over Na₂SO₄ and concentrated. Flash chromatography on silica gel using a gradient of 100:2:0.5 to 100:3:0.5 CH₂Cl₂/MeOH/NH₄OH gave the title compound (0.42 g).

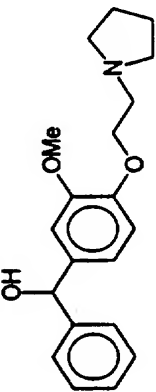
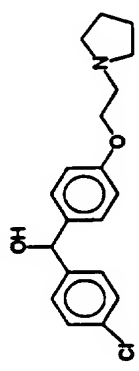
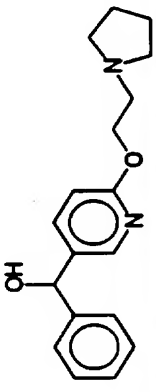
Example 99

20 To a stirred solution of the ketone of example 50 (850 mg) in EtOH (25 ml) was added water (5 ml), then NaBH₄ (513 mg) was added pinch by pinch and the mixture stirred at room temperature for 2 hours. The reaction mixture was quenched with 1 N NaOH, extracted with ethyl acetate, dried over MgSO₄ and concentrated. The residue was chromatographed over silica gel using 4/95/1 EtOH/CH₂Cl₂/NH₄OH to give the title product (500 mg).

30 Analysis Calculated for C₁₉H₂₁ FN O₂
Calculated: C, 72.35; H, 7.03; N, 4.44
Found: C, 72.01; H, 7.01; N, 4.38

Ex. No.	Compound	Starting Ketone	Analysis
104	 OH CH ₃ O N	Ex. 56	HRMS (M+) for C ₂₀ H ₂₈ NO ₂ Calc: 311.1885 Found: 311.1856
105	 OH CH ₃ O N F	Ex. 57	HRMS (M+) for C ₂₀ H ₂₈ NO ₂ Calc: 311.1885 Found: 311.1882
106	 OH F O N F	Ex. 58	HRMS (M+) for C ₁₉ H ₂₁ F ₂ NO ₂ Calc: 333.1540 Found: 333.1529
107	 OH F O N F F	Ex. 59	HRMS (M+) for C ₁₉ H ₂₁ F ₃ NO ₂ Calc: 333.1540 Found: 333.1548
108	 OH CO ₂ Me O N	Ex. 60	HRMS (M+) for C ₂₁ H ₂₈ NO ₄ Calc: 355.1784 Found: 355.1808

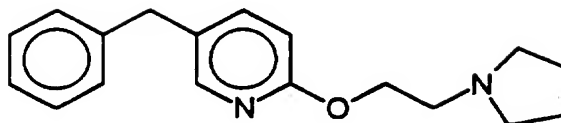
-129-

Ex. No.	Compound	Starting Ketone	Analysis
109		Ex. 61	HRMS (M+) for C ₂₀ H ₂₆ NO ₃ Calc: 327.1834 Found: 327.1807
110		Ex. 51	C ₁₇ H ₂₂ ClNO ₂ Calc: C, 68.77; H, 6.68; N, 4.22; Cl, 10.68 Found: C, 68.48; H, 6.75; N, 4.17; Cl, 10.62
111		Ex. 73	C ₁₈ H ₂₂ N ₂ O ₂ · 0.4 H ₂ O: Calc: C, 70.75; H, 7.52; N, 9.17. Found: C, 70.63; H, 7.52; N, 9.08.

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Example 112

5



This example demonstrates the reduction of benzylic alcohols using hydrogenation in the presence of palladium.

10 The product of example 111 (250 mg, 0.84 mmol) was dissolved in 20 ml of 60% MeOH\40% acetic acid and transferred to a Parr shaker along with a catalytic amount of 4% Pd\C. The reaction was shaken for 5 hours at room temperature under a 5 psi pressure of H₂. The reaction mixture was filtered and basified with 10% NaOH. The mixture was extracted with 2 25 ml portions of EA which were combined. The organic layer was dried and the solvent removed in vacuo to afford pure product.

20

Analysis calculated for C₁₈H₂₂N₂O 0.25 H₂O:

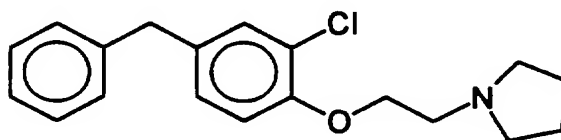
Calculated: C, 75.36; H, 7.91; N, 9.76.

Found: C, 75.43; H, 8.13; N, 9.45.

25

Example 113

30



This example demonstrates reduction of benzylic alcohols using triethylsilane.

35 To a stirred solution of the product from Example 100 (0.26 g, 0.78 mmol) and triethylsilane (1 mL) in methylene chloride (5 mL) was added trifluoroacetic acid (0.1 mL) in one portion. This solution was

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stirred 10 minutes at room temperature. The mixture was poured into 5% aqueous Na_2CO_3 (25 mL) and extracted with 25 mL of ethyl acetate. The ethyl acetate was washed 2 times with water (2 x 10 mL), saturated brine (10 mL) and dried over MgSO_4 . After filtration, the volatile components were removed at reduced pressure on a rotary evaporator. The crude product was chromatographed on silica gel gradient eluting with ethyl acetate:hexane (1:9 to 1:1) saturated with aqueous concentrated ammonium hydroxide. This produced 0.22 g (89%) of the title compound.

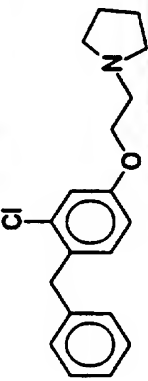
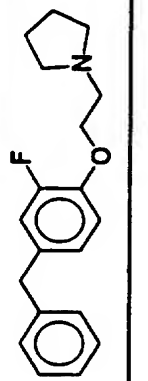
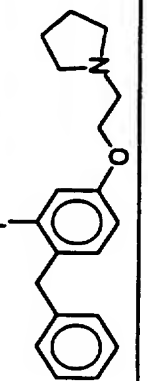
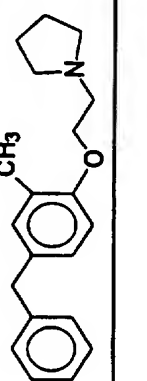
HRMS (M^+) for $\text{C}_{19}\text{H}_{22}^{35}\text{ClNO}$
Calculated: 315.1390
15 Found: 315.1385

In the same manner as described in example 112 the compounds described in Table 8 were reduced.

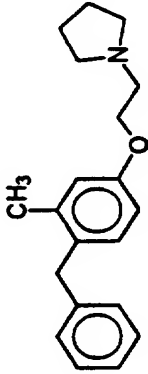
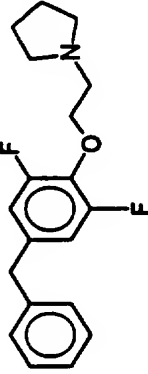
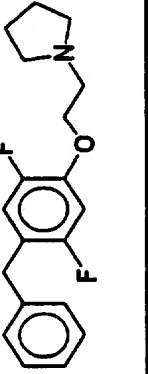
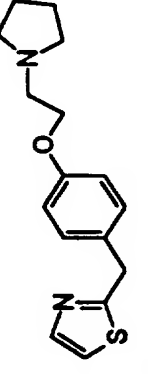
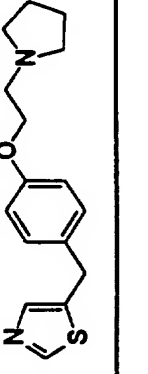
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TABLE 8



Ex. No.	Compound	Starting Alcohol	Analysis
114		Ex. 101	HRMS (M+) for C ₁₉ H ₂₂ ³⁶ ClNO Calc: 315.1390 Found: 315.1388
115		Ex. 102	HRMS (M+) for C ₁₉ H ₂₂ FNO Calc: 299.1685 Found: 299.1678
116		Ex. 103	HRMS (M+) for C ₁₉ H ₂₂ FNO Calc: 299.1685 Found: 299.1681
117		Ex. 104	HRMS (M+) for C ₂₀ H ₂₅ NO Calc: 295.1936 Found: 295.1945

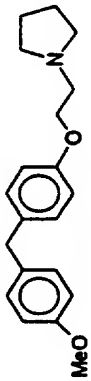
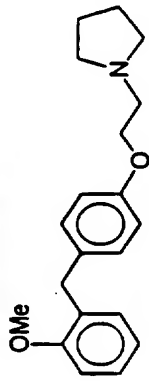
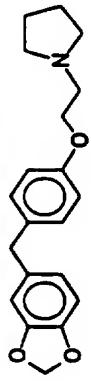
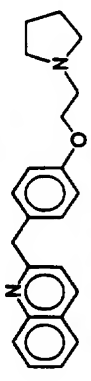
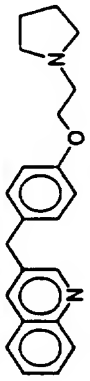
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Ex. No.	Compound	Starting Alcohol	Analysis
118		Ex. 105	HRMS (M+) for C ₂₀ H ₂₅ NO Calc: 295.1936 Found: 295.1914
119		Ex. 106	HRMS (M+) for C ₁₉ H ₂₁ F ₂ NO Calc: 317.1591 Found: 317.1593
120		Ex. 107	HRMS (M+) for C ₁₉ H ₂₁ F ₂ NO Calc: 317.1591 Found: 317.1598
121		Ex. 97	HRMS, m/z 288.1290 (calc'd for C ₁₆ H ₂₀ SON ₂ , 288.1297).
122		Ex. 98	HRMS, m/z 288.1299 (calc'd for C ₁₆ H ₂₀ SON ₂ , 288.1296).

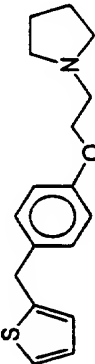
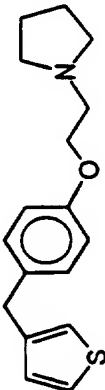
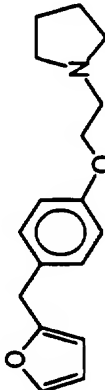
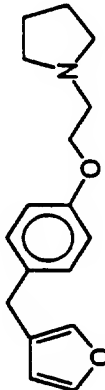
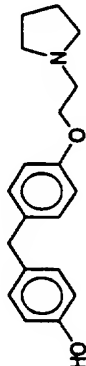
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Ex. No.	Compound	Starting Alcohol	Analysis
123		Ex. 108	HRMS (MH+) for C ₂₁ H ₂₆ NO ₃ Calc: 340.1913 Found: 340.1885
124		Ex. 109	HRMS (MH+) for C ₂₀ H ₂₆ NO ₂ Calc: 311.1885 Found: 311.1875
125		Ex. 77	C ₁₉ H ₂₂ N ₂ O 0.2H ₂ O: Calc: C, 75.60; H, 7.89; N, 9.80. Found: C, 75.53; H, 7.69; N, 9.58. M ⁺ = 282.
126		Ex. 78	C ₁₉ H ₂₂ N ₂ O 0.3H ₂ O: Calc: C, 75.12; H, 7.92; N, 9.73. Found: C, 74.96; H, 7.14; N, 9.47. M ⁺ = 282.
127		Ex. 79	C ₂₀ H ₂₆ NO ₂ 0.4H ₂ O: Calc: C, 75.39; H, 8.16; N, 4.40. Found: C, 75.20; H, 8.13; N, 4.43. M ⁺ = 311.

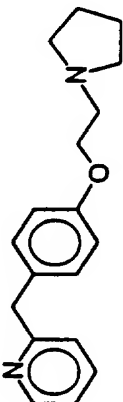
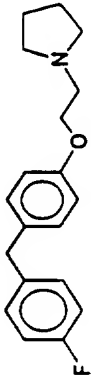
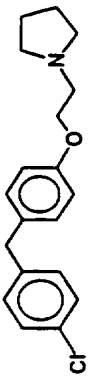
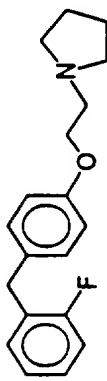
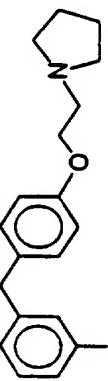
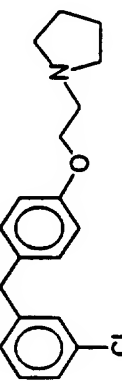
- 135 -

Ex. No.	Compound	Starting Alcohol	Analysis
128		Ex. 80	$C_{20}H_{26}NO_2 \cdot 0.2H_2O$: Calc: C, 76.25; H, 8.13; N, 4.45. Found: C, 76.11; H, 7.88; N, 4.41. $M^+ = 311$.
129		Ex. 88	$C_{20}H_{26}NO_2$: Calc: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.18; H, 7.61; N, 4.11. $M^+ = 311$.
130		Ex. 82	$C_{20}H_{23}NO_4 \cdot 0.2H_2O$: Calc: C, 69.63; H, 6.84; N, 4.06. Found: C, 69.75; H, 6.88; N, 4.09. $M^+ = 325$.
131		Ex. 83	$M^+ = 332$.
132		Ex. 84	$C_{22}H_{24}N_2O_0.5H_2O$: Calc: C, 74.39; H, 7.38; N, 8.20. Found: C, 77.42; H, 7.31; N, 8.26.

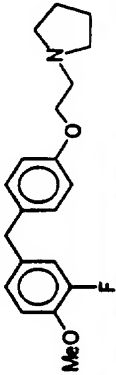
-136-

Ex. No.	Compound	Starting Alcohol	Analysis
133		Ex. 84	C ₁₇ H ₂₁ NOS: Calc: C, 71.04; H, 7.34; N, 4.87. Found: C, 70.57; H, 7.45; N, 4.77. M ⁺ = 287.
134		Ex. 85	C ₁₇ H ₂₁ NOS.0.2H ₂ O: Calc: C, 70.16; H, 7.41; N, 4.81. Found: C, 70.15; H, 7.07; N, 4.83. M ⁺ = 287.
135		Ex. 86	M ⁺ = 271.
136		Ex. 87	M ⁺ = 271.
137		Ex. 90	C ₁₉ H ₂₃ NO ₂ .0.3H ₂ O: Calc: C, 75.37; H, 7.86; N, 4.63. Found: C, 75.23; H, 7.24; N, 4.14. M ⁺ = 297.

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Ex. No.	Compound	Starting Alcohol	Analysis
138		Ex. 92*	HRMS for $C_{19}H_{22}N$ Calc: 282.1732 Found: 282.1726
139		Ex. 99	$C_{19}H_{22}FNO \cdot 1/4 H_2O$ Calc: C, 75.10; H, 7.46; N, 4.61 Found: C, 75.31; H, 7.32; N, 4.54
140		Ex. 110	$C_{19}H_{22}ClNO$ Calc: C, 72.24; H, 7.02; N, 4.44 Found: C, 72.02; H, 7.34; N, 4.30
141		Ex. 93	$C_{19}H_{22}FNO$ Calc: C, 76.23; H, 7.41; N, 4.69 Found: C, 76.29; H, 7.34; N, 4.64
142		Ex. 94	$C_{19}H_{22}FNO$ Calc: C, 76.23; H, 7.41; N, 4.69 Found: C, 76.11; H, 7.67; N, 4.66
143		Ex. 95	$C_{19}H_{22}ClNO \cdot 0.25 H_2O$ Calc: C, 71.24; H, 7.06; N, 4.37; Cl, 11.07 Found: C, 71.18; H, 7.18; N, 4.38; Cl, 10.95

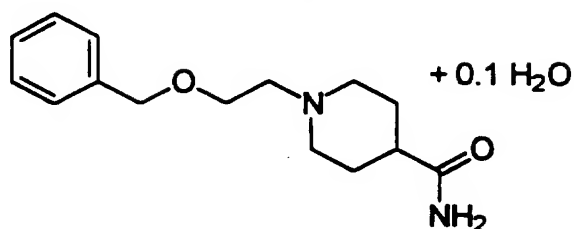
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Ex. No.	Compound	Starting Alcohol	Analysis
144		Ex. 96	$C_{20}H_{24}FNO_2 \cdot 0.1 H_2O$ Calc: C, 72.53; H, 7.36; N, 4.23 Found: C, 72.42; H, 7.64; N, 4.12 $M^+ = 329$

5

* The alcohol of Example 93 was converted to its corresponding acetate with Ac_2O and then hydrogenated

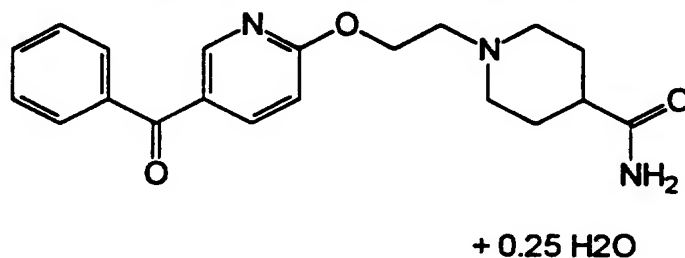
- 139 -

Example 145

To a stirred solution of 15.2 g of 2-benzyloxyethanol in 100 ml of CH_2Cl_2 and 50 ml pyridine was added 20 g of p-toluenesulfonyl chloride and 20 mg of N,N-dimethylaminopyridine at 0°C . The mixture was stirred at 0°C for 10 minutes, warmed up to 25°C and stirred at 25°C for 4 hrs, and concentrated in vacuo. The residue was extracted with ethyl acetate, washed with water, dried over Na_2SO_4 and concentrated in vacuo gave crude oily gum which was flash chromatographed on silica to give 6.5 g of corresponding tosylate which was reacted with isonipecotamide to provide the title compound following the procedure described in example 10.

Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_2 \cdot 0.1\text{H}_2\text{O}$: C, 68.20; H, 8.47; N, 10.61

Found: C, 68.28; H, 8.31; N, 10.44

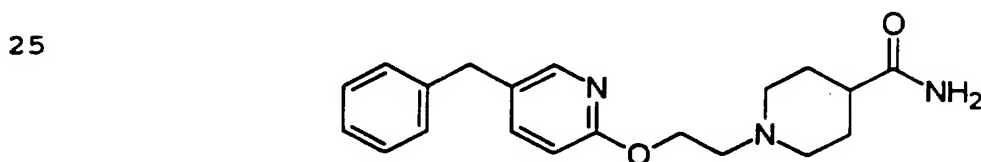
Example 146Preparation of 1-[2-[(5-benzoylpyridin-2-yl)oxy]ethyl]-4-piperidinecarboxamide

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A solution of 1.5 g of the compound of example 145 in 25 ml of ethanol in a parr shaker was exposed to hydrogen gas at 25°C at 60 psi pressure for 23 hrs. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to afford an oily gum. To a stirred solution of 344 mg of the gum in 6 ml of DMF was added 200 mg of 50% NaH (in oil) and the mixture was stirred at 25° C for 15 minutes under nitrogen atmosphere. 436 mg of the compound of example 73 was added to the mixture and was stirred at 25°C for 4 hrs, quenched with water and the mixture was poured into water and was extracted with ethyl acetate. The organic extract was washed with water, dried over Na₂SO₄ and concentrated in vacuo to give 380 mg of oily residue, which was chromatographed on silica gel using 85% CHCl₃, 14% ethanol and 1% NH₄OH as eluant to provide 14 mg of title compound as white crystalline solid.

Calcd for C₂₀H₂₃N₃O₃·1/4H₂O: C, 67.11; H, 6.62; N, 11.74
Found: C, 67.17; H, 6.94; N, 11.63

Example 147



To a stirred solution of 365 mg of the compound prepared in example 146 in 5 ml of ethanol was added 365 mg of NaBH₄ and the mixture was stirred at room temperature for 1 hr. The mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with water, dried over Na₂SO₄, concentrated in vacuo to yield crude residue. The crude residue was chromatographed on silica gel using 80% CHCl₃, 19% ethanol and 1% NH₄OH as eluant to provide

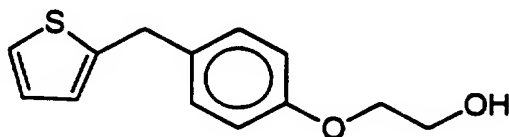
- 141 -

210 mg of an oily gum. To a solution of the oily gum in 10 ml of ethanol containing 1 ml of glacial acetic acid, in a parr shaker was exposed to hydrogen gas at 25°C over 10% Pd/C catalyst at 5 psi pressure for 6 hrs. The catalyst was removed by filtration and the solvent was removed from the filtrate under reduced pressure to give an oily residue. The oily residue was extracted with ethyl acetate, washed with 10% K₂CO₃ solution and water, dried over Na₂SO₄, concentrated in vacuo to provide a residue which was chromatographed on silica gel using 85% CHCl₃, 14% ethanol and 1% NH₄OH as eluant to provide 110 mg of the title compound 57 as white solid.

Calcd for C₂₁H₂₅N₃O₂ .1/4 H₂O: C, 69.84; H, 7.47; N, 12.22

Found: C, 69.39; H, 7.78; N, 11.98

Example 148



The phenol of example 18 (90 mg, 0.47 mmol) was dissolved in DMF (2 mL). To this was added tetrabutylammonium bromide (16 mg, 0.05 mmol) and ethylene carbonate (62 mg, 0.71 mmol). The mixture was heated at 140°C under Argon for 4 hours. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with brine, dried (Na₂SO₄) and concentrated to provide the title compound as

- 142 -

yellow oil. The resulting product had the following properties: ^1H NMR: 300 MHz spectrum consistent with proposed structure.

5 Analysis Calculated for $\text{C}_{13}\text{H}_{14}\text{O}_2\text{S} \cdot 0.7\text{H}_2\text{O}$:

Calc: C, 63.23; H, 6.29.

Found: C, 63.20; H, 5.83.

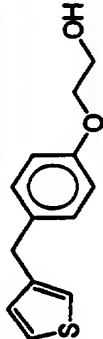
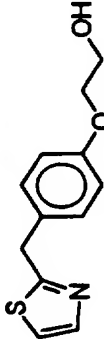
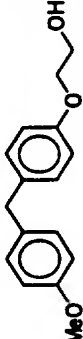
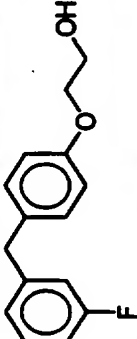
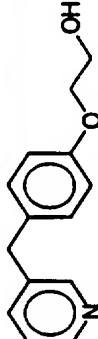
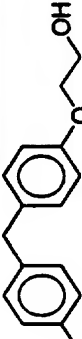
$\text{M}^+ = 234$

- 10 The compounds exemplified in the following Table were prepared essentially as described in Example 148, except that the phenol of example 18 was replaced with the corresponding phenol designated in the Table.

15

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TABLE 9

Ex. No.	Compound	Starting Phenol	Analysis
149		Ex. 19	$C_{13}H_{14}O_2S$ Calc: C, 66.64; H, 6.02. Found: C, 66.26; H, 6.16. $M^+ = 234$
150		Ex. 20	Compound was fully characterized in the next step. See Example No. 231.
151		Ex. 21	$C_{18}H_{18}O_3$ Calc: C, 74.40; H, 7.02 Found: C, 73.97; H, 6.65 $M^+ = 258$
152		Ex. 22	Compound was fully characterized in the next step. See Example No. 233.
153		Ex. 24	Compound was fully characterized in the next step. See Example No. 236.
154		Ex. 29	Compound was fully characterized in the next step. See Example No. 234.

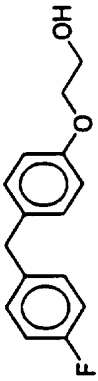
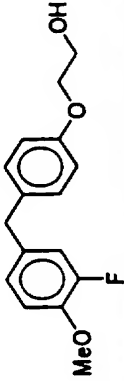
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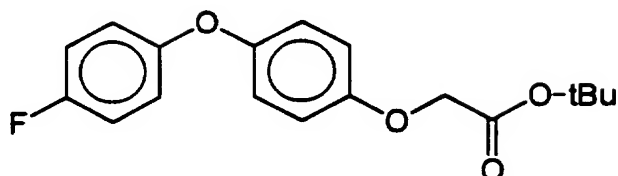
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Ex. No.	Compound	Starting Phenol	Analysis
155		Ex. 25	Compound was fully characterized in the next step. See Example No. 235.
156		Ex. 23	Compound was fully characterized in the next step. See Example No. 314.

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Example 157

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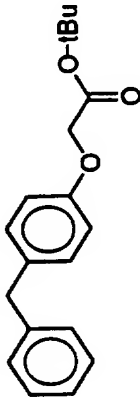
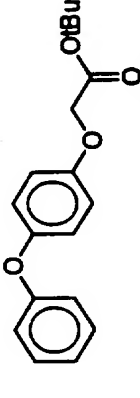
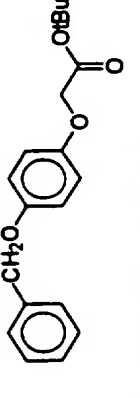
To a solution of the product from Example 48 (2.04 g, 10 mmol) in 25 mL DMF was added t-butyl bromoacetate (1.9 mL, 11.8 mmol) and catalytic n-Bu₄NI, followed by 60% NaH dispersion in oil (0.48 g, 12 mmol). The mixture was heated at 60°C for 3.5 hours and cooled. The mixture was poured into ether and water and the ether layer separated, washed with brine, dried over Na₂SO₄ and concentrated. Flash chromatography on silica using 20:1 hexane/EtOAc to provide the title compound (2.84 g, 89%) as a colorless oil.

Anal. calc'd for C₁₈H₁₉FO₄:

20	Calculated:	C, 67.91; H, 6.02.
	Found:	C, 67.67; H, 6.18.

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TABLE 10

Ex. No.	Compound	Starting Phenol	Analysis
158		4-hydroxy-diphenylmethane	NMR spectrum consistent with proposed structure.
159		4-phenoxyphenol	NMR spectrum consistent with proposed structure.
160		4-(benzyloxy)phenol	$C_{18}H_{20}O_4$ Calc: C, 72.59; H, 7.05. Found: C, 72.28; H, 7.18.

5

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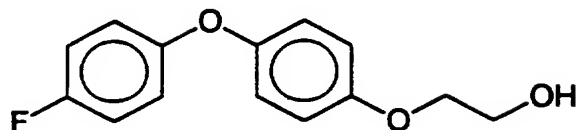
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Example 161

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10

To a solution of the product from Example 157 (2.7 g, 8.48 mmol) in THF (50 mL) was added solid LAH (0.38 g, 10 mmol) in portions and the mixture stirred at 25°C for 30 minutes. The mixture was poured into EtOAc and water and the EtOAc layer separated, washed with brine, dried over Na₂SO₄ and concentrated to provide the title compound (2.08 g, 99%) as a white solid: mp 78-79°C;

15

Anal. calc'd for C₁₄H₁₃FO₃·0.2 H₂O:

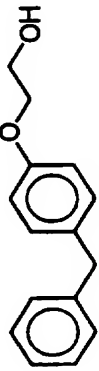
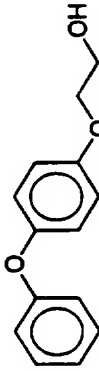
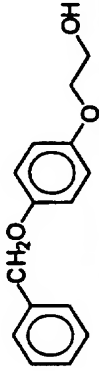
Calculated: C, 66.77; H, 5.36.

Found: C, 66.97; H, 5.38.

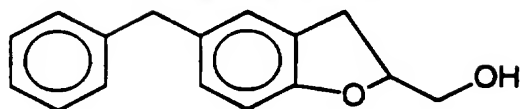
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TABLE 11

Ex. No.	Compound	Starting tBu Ester	Analysis
162		Ex. 158	NMR spectrum consistent per the proposed structure
163		Ex. 159	NMR spectrum consistent per the proposed structure
164		Ex. 160	$C_{16}H_{18}O_3 \cdot 0.15 H_2O$: Calc: C, 72.94; H, 6.65. Found: C, 72.92; H, 6.58.

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Example 165

5

To a stirred solution of 4-hydroxy-diphenylmethane (20 g, Aldrich) in CH₂Cl₂ (100 mL) was added 50% aqueous solution of NaOH (50 mL) followed by allyl bromide (15 mL, Aldrich) and tetraethylammonium bromide (1 g),

10 After 16 hours, the layers were separated. The aqueous phase was extracted with ether. The combined organic extract was dried over MgSO₄ and distilled to give 4-allyloxy-diphenylmethane (16 g). B.p. 130-135°C/1 mm. This product (16 g) was heated to 230°C for 8 hours.

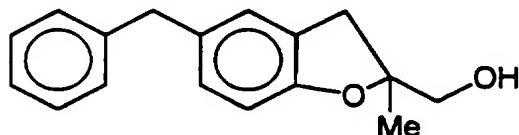
15 After cooling, the resulting product was taken-up in CHCl₃ (500 mL). The solution was stirred and cooled to 0°C. To this was added 3-chloroperoxybenzoic acid (16 g, 80-85%, Aldrich) suspended in CHCl₃ (100 mL). After 2 hours, the mixture was filtered through celite and the

20 filtrate washed with saturated NaHCO₃ solution. The organic extract was dried over MgSO₄, and heated to reflux with 1-methyl-morpholine (10 mL) for 15 minutes. The mixture was concentrated and the residue

25 chromatographed over silica gel using 30% ethyl acetate in hexane to give the title product (10 g) as a colourless thick oil.

Example 166

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35 To a stirred solution of 4-hydroxy-diphenylmethane (25 g, Aldrich) in CH₂Cl₂ (200 mL) was added 50% aqueous solution of NaOH (50 mL) followed by 3-chloro-2-

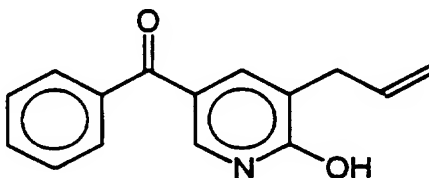
- 150 -

methypropene (50 mL, Aldrich) and tetrabutylammonium bromide (1 g), After 16 hours, the layers were separated. The aqueous phase was extracted with ether. The combined organic extract was dried over MgSO_4 and
5 distilled to give 4-methallyloxy-diphenylmethane (16 g). B.p. $135^\circ\text{C}/1\text{ mm}$.
The product (8.8 g) was heated to $215\text{--}220^\circ\text{C}$ for 8 hours. After cooling, the resulting product was chromatographed over silica gel using 6% ethyl acetate
10 in hexane to give the corresponding rearranged product (8 g). This material was taken-up in CHCl_3 (500 mL). The solution was stirred and cooled to 0°C . To this was added Na_2CO_3 (4 g) and 3-chloroperoxybenzoic acid (9 g, 80-85%, Aldrich) suspended in CHCl_3 (100 mL).
15 After 4.5 hours, the mixture was filtered through celite and the filtrate washed with 5% aqueous Na_2CO_3 solution. The organic extract was dried over MgSO_4 and concentrated to 100 mL. To this solution was added para-toluenesulphonic acid (0.5 g) and the mixture let
20 stand at room temperature for 16 hours. The solution was then concentrated and the residue chromatographed over silica gel using 30% ethyl acetate in hexane to give the title product (10 g) as a colorless thick oil.

25

Example 167

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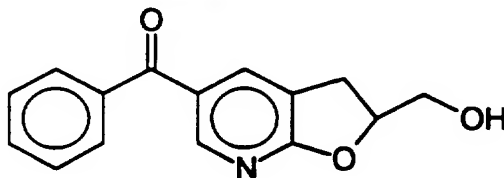


35

A 60% mineral oil suspension of sodium hydride (1.9 g) was washed with hexane and suspended in THF (200 mL) at -78°C . To this stirred solution was added allyl alcohol (3 mL). After 1 hour, the product of

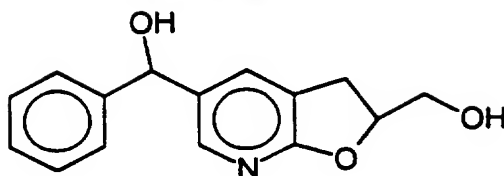
- 151 -

Example 73 was added in one lot and the mixture stirred for 16 hours. Then allyl alcohol (5 mL) was added and the mixture refluxed for 0.25 hours. The mixture was cooled, washed with water, dried over MgSO_4 , and concentrated to give a thick liquid. A solution of this material in diphenylether (20 ml) was heated to reflux for 5 hours. The mixture was cooled and chromatographed over silica gel using 80-100% ethyl acetate in hexane to give the title product (1.8 g) as a white solid.

Example 168

To a stirred solution of the product of Example-167 (1.1 g) in CHCl_3 (20 mL) at 0°C was added 3-chloroperoxybenzoic acid (1.5 g, 50-60%, Aldrich) suspended in CHCl_3 (5 mL). After 2 hours, 3-chloroperoxybenzoic acid (0.5 g, 80-85%, Aldrich) was added to the reaction mixture. After 4 hours, the mixture was allowed to warm to room temperature over 1hr. The mixture was washed with 5% aqueous K_2CO_3 solution, dried over MgSO_4 , and concentrated. The residue was chromatographed over silica gel using 50% ethyl acetate in hexane as eluant to give a mixture of an epoxide and the title product. This mixture in ethyl acetate (20 mL) was allowed to stand at room temperature with para-toluenesulfonic acid (20 mg) for 16 hours. The solution was washed with water, dried over MgSO_4 , and concentrated to give the title product as a white solid (0.85 g).

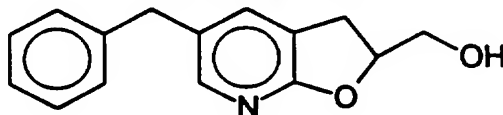
- 152 -

Example 169

5

To a stirred solution of the product of Example 168 (0.8 g) in THF (50 mL) was added sodium borohydride (0.4 g) and the mixture refluxed for 1 hour. The mixture was treated with saturated aqueous NH_4Cl with caution and extracted with ethyl acetate. The organic phase was washed with water, dried over MgSO_4 to give the title product as a colorless solid.

15

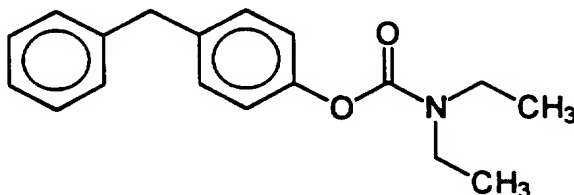
Example 170

20

The product of Example 169 was hydrogenated in a parr apparatus in a mixture of ethyl acetate and acetic acid over 5% Pd on carbon under 5 psi hydrogen atmosphere at room temperature for 3 hours. The reaction mixture was filtered and the filtrate concentrated. The residue was chromatographed over silica gel using ethyl acetate as eluant to give the title product as a colorless solid (0.3 g).

25

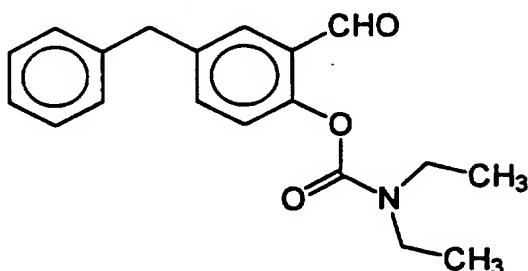
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Example 171

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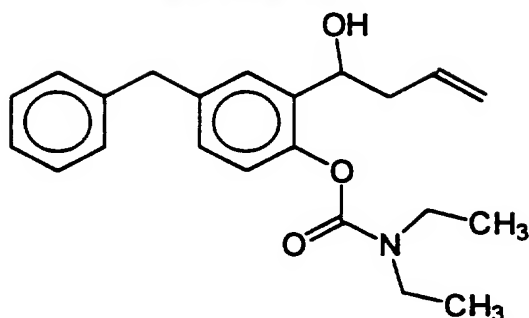
- 153 -

A 35% mineral oil suspension of potassium hydride (12 g) was washed with hexane and suspended in THF (150 mL) at -78°C. The mixture was stirred and 4-hydroxydiphenylmethane (18.5 g) was added as solid in several portions over 0.5 hours. The mixture was allowed to warm to 0°C over 2 hours and cooled back to -78°C. To this was added diethylcarbamoylchloride (13.6 g, Aldrich) over 0.25 hours and the mixture allowed to warm to room temperature over 16 hours. The mixture was refluxed for 0.5 hours and cooled in ice. To this was added water and the organic phase was dried over MgSO₄ and distilled to give the title product as a colorless liquid. B.p. 170-175°C/0.05 mm.

Example 172

To a stirred solution the product of Example 171 (5.085 g) in ether (150 mL) and tetramethylethylenediamine (3 mL) at -78°C was added a 1.3 molar solution of sec.butyl lithium in cyclohexane (16 mL). After 1 hour, dimethylformamide (1.45 mL) was added. After 2 hours, saturated aqueous NH₄Cl was added and the layers separated. The organic phase was dried over MgSO₄ and concentrated. The residue was chromatographed over silica gel using 20% ethyl acetate in hexane to give the title product as thick oil (5.1 g).

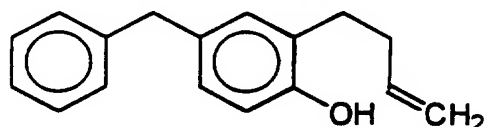
- 154 -

Example 173

10

The product of Example 172 was taken-up in ether (125 mL) and the solution cooled to -78°C. To this stirred solution was added a 1N ether solution of allylmagnesium bromide (16 mL). After 10 minutes, the mixture was warmed to 0°C and quenched carefully with saturated aqueous NH₄Cl. The layers were separated and the organic phase was dried over MgSO₄ and concentrated. The residue was chromatographed over silica gel using 20% to 30% ethyl acetate in hexane to give the title product as a thick gum (3.9 g).

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Example 174

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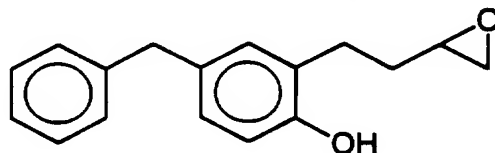
To a stirred solution of the product of Example 173 (1.24 g) in THF (30 mL) at 0°C was added sulfur trioxide-pyridine complex (0.812 g, Aldrich). After 0.5 hours, the mixture was allowed to stand at 4°C for 16 hours. Then the mixture was stirred at 0°C for 4 hours and cooled to -78°C. To this mixture was added lithium aluminium hydride (1 g) in one lot. The mixture was allowed to warm to 0°C over 1 hour, then to room temperature over 3 hours. To this was added, carefully, water and then excess of 1N HCl. The mixture was extracted with ether. The combined organic

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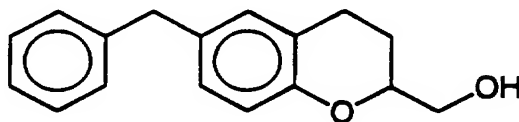
extract was dried and concentrated to give the title product as a thick gum (0.38 g).

Example 175



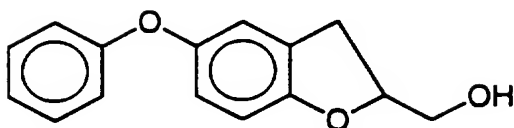
To a stirred solution of the product of Example-174 (0.38 g) in CHCl_3 (5 mL) at 0°C was added 3-chloroperoxybenzoic acid (0.38 g, 80-85%, Aldrich) suspended in CHCl_3 (3 mL). After 1 hour 3-chloroperoxybenzoic acid (0.38 g, 80-85%, Aldrich) was added. After 1 hour, the mixture was washed with saturated NaHCO_3 . The organic phase was dried by gravity filtration and concentrated. The residue was chromatographed over silica gel using 20% ethyl acetate in hexane to give the title product as a colorless gum (0.18 g).

Example 176



A solution of the product of Example 175 (0.18 g) and para-toluenesulphonic acid (5 mg) in CHCl_3 (5 mL) was allowed to stand at room temperature for 16 hours. The solution was washed with water and dried over MgSO_4 to give the title product as a thick gum.

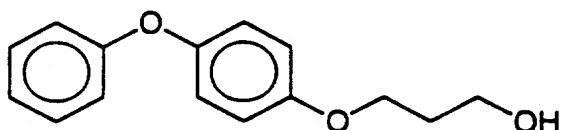
- 156 -

Example 177

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The procedure of Example 166 was repeated using 4-phenoxyphenol (Aldrich) and allyl bromide in the place of 4-hydroxy-diphenylmethane and 3-chloro-2-methylpropane respectively to obtain the title compound as a thick liquid.

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Example 178

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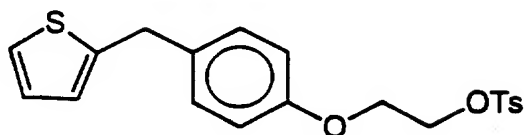
4-Phenoxyphenol (4.66g, 25 mmol), 3-chloro-1-propanol (2.51g, 26.5 mmol), and tetrabutylammonium iodide (82mg, 0.22 mmol) were dissolved in 50 mL DMF. Sodium hydride (1.33g, 33.2 mmol, 60% dispersion in mineral oil) was added slowly to the reaction mixture which was stirred at 60°C for 12 hours. The reaction was poured into 400 mL water and extracted with 4 X 150 mL ethyl acetate. The combined organic phases were dried (MgSO₄), filtered and concentrated to afford a brown oil. The crude oil was chromatographed (silica gel, 20% ethyl acetate/hexane) to give the pure product as white crystals (3.58g, 59%). The product had the following properties: Anal. calcd for C₁₅H₁₆O₃: C, 73.75; H, 6.60. Found C, 73.36; H, 6.65.

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Example 179

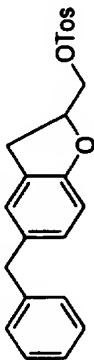
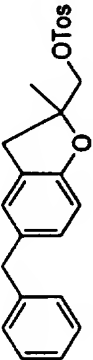
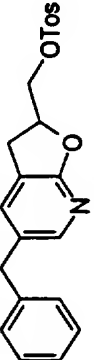
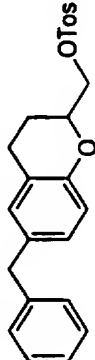
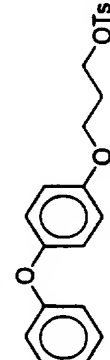
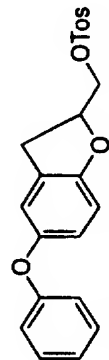
5

The alcohol of example 148 (90 mg, 0.38 mmols) was dissolved in a mixture of CH_2Cl_2 (2 mL) and pyridine. The solution was cooled to 0° under Argon, and then p-toluenesulfonyl chloride (87 mg, 0.46 mmol) followed by DMAP (3 mg) were added to the mixture. The reaction mixture was stirred at 0°C for 0.5 hours, and then warmed up to room temperature and stirred for 16 hours. The solvent was removed under reduced pressure. The residue was dissolved in ether, washed with saturated KHSO_4 and brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated to give 120 mg of the title compound as yellow oil.

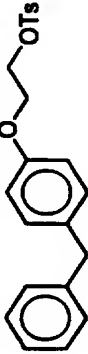
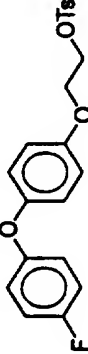
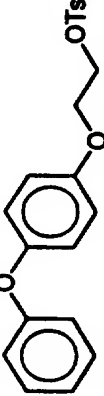
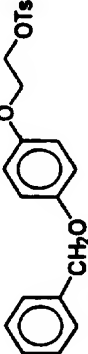
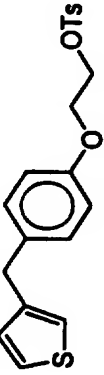
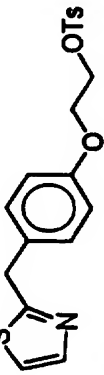
The compounds in Table 12 were made in an analogous manner. The resulting product was fully characterized in the next step. See Example No. 229.

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TABLE 12

Ex. No.	Compound	Starting Alcohol	Analysis
180		Ex. 165	Compound was characterized by NMR and structure confirmed by the analysis of compound of Example 282
181		Ex. 166	Compound was characterized by NMR and structure confirmed by the analysis of compound of Example 285
182		Ex. 170	Compound was characterized by NMR and structure confirmed by the analysis of compound of Example 287
183		Ex. 176	Compound was characterized by NMR and structure confirmed by the analysis of compound of Example 293
184		Ex. 178	Compound was characterized by NMR and structure confirmed by the analysis of compound of Example 350
185		Ex. 177	Compound was characterized by NMR and structure confirmed by the analysis of compound of Example 291

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Ex. No.	Compound	Starting Alcohol	Analysis
186		Ex. 162	Compound was fully characterized in the next step. See Example No. 238.
187		Ex. 161	C ₂₁ H ₁₉ SFO ₆ : Calc: C, 62.68; H, 4.76. Found: C, 62.73; H, 4.85.
188		Ex. 163	Compound was fully characterized in the next step. See Example No. 252.
189		Ex. 164	Compound was fully characterized in the next step. See Example No. 198.
190		Ex. 149	Compound was fully characterized in the next step. See Example No. 230.
191		Ex. 150	Compound was fully characterized in the next step. See Example No. 231.

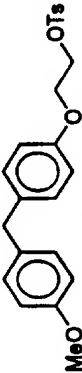
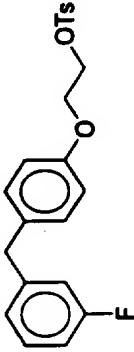
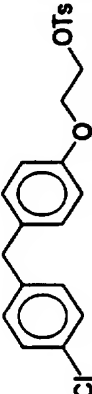
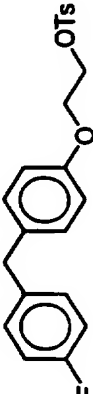
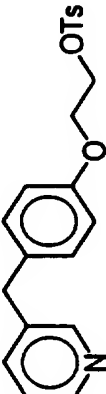
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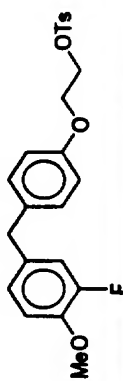
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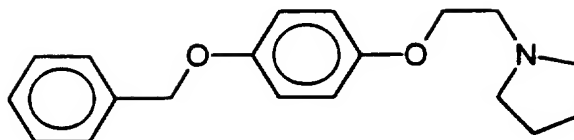
-160-

Ex. No.	Compound	Starting Alcohol	Analysis
192		Ex. 151	Compound was fully characterized in the next step. See Example No. 232.
193		Ex. 152	Compound was fully characterized in the next step. See Example No. 233.
194		Ex. 154	C ₂₁ H ₁₈ SFO ₆ : Calc: C, 62.68; H, 4.76. Found: C, 62.73; H, 4.85.
195		Ex. 163	Compound was fully characterized in the next step. See Example No. 235.
196		Ex. 153	Compound was fully characterized in the next step. See Example No. 236.

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Ex. No.	Compound	Starting Alcohol	Analysis
197	 <chem>COc1cc(F)ccc1Cc2ccc(OCCOS(=O)(=O)c3ccc(C)cc3)cc2</chem>	Ex. 88	Compound was fully characterized in the next step. See Example No. 314.

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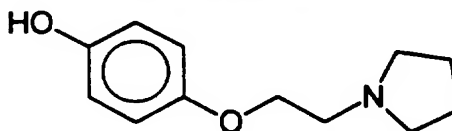
Example 198

5
10 4-(Benzyloxy)phenol (0.41g, 2.05 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (0.36g, 2.1 mmol) and powdered potassium carbonate (1.09g, 7.9 mmol) were stirred in 23 mL of N,N-dimethylformamide at 80°C for 12 hours. The reaction was cooled to room temperature and poured into 300 mL water. The aqueous phase was
15 extracted with 4 X 50 mL ethyl acetate. The combined organic washes were dried (NaSO₄), filtered, and concentrated to afford 0.43 g amber oil. The crude product was chromatographed (silica gel, 20% methanol/heptane) to give the pure product (0.39 g,
20 64%) as a pale yellow solid. The product had the following properties:

Analysis calculated for C₁₉H₂₃NO₂·0.10 H₂O:

Calc: C, 76.27; H, 7.82; N, 4.68.

25 Found: C, 76.09; H, 7.80; N, 4.62.

Example 199

30 The product from Example 198 (2.78 g, 9.3 mmol) was dissolved in 35 mL THF in a Parr Shaker apparatus. A catalytic amount of 4% Pd/C was added, and the
35 reaction was run under 60 p.s.i. of H₂ at room temperature for 23 hours. The reaction was filtered

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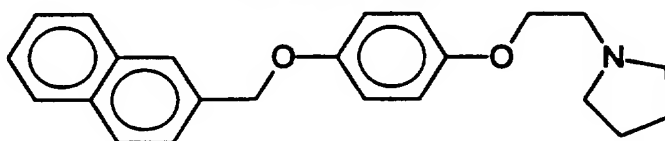
through Celite and concentrated to afford the product (1.49 g, 78%) as yellow crystals. The product had the following properties: mp 113-115°.

5 Analysis calculated for $C_{12}H_{17}NO_2 \cdot 0.25H_2O$:

Calc: C, 68.06; H, 8.33; N, 6.61.

Found: C, 68.16; H, 8.06; N, 6.55.

Example 200



2-(Bromomethyl)naphthalene (0.36g, 1.6 mmol), the phenol from Example 199 (0.33g, 1.6 mmol) and powdered potassium carbonate (0.52, 3.8 mmol) were stirred in 15 mL DMF at 80° for 12 hours. The reaction was cooled to room temperature and poured into 200 mL water. The aqueous phase was extracted with 4 X 30 mL ethyl acetate. The combined organic washes were dried (NaSO₄), filtered, and concentrated to afford a tan solid which was recrystallized from ethyl acetate/hexane to give the pure product (67 mg, 12%).

The product had the following properties:

H.R.M.S. M^+ calculated for $C_{23}H_{27}NO_7$:

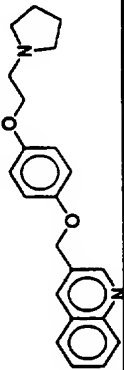
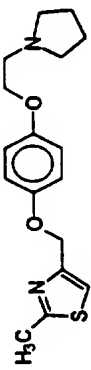
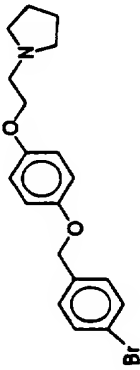
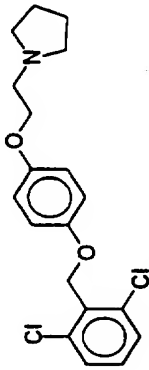
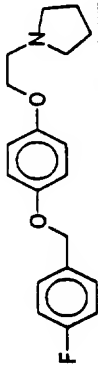
Calc: 347.1886.

Found: 347.1856.

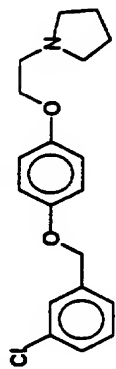
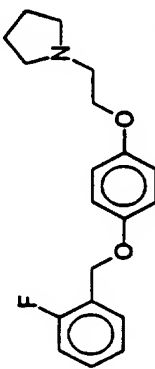
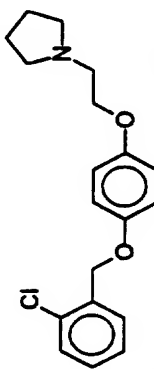
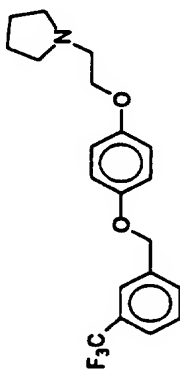
The compounds exemplified in the following Table were prepared essentially as described in Example 200 except that 2-(Bromoethyl)naphthalene was replaced by the designated Ar¹ Precursor.

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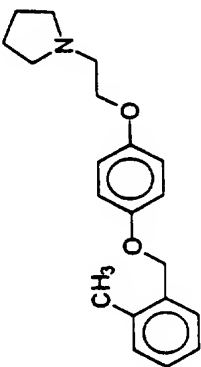
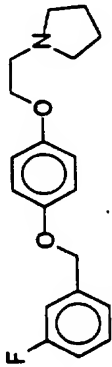


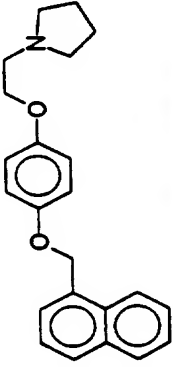
TABLE 13

Ex. No.	Compound	Ar ¹ Precursor	Chrom.	Analysis
201		2-(chloromethyl)quinoline monohydrochloride	silica gel, methanol/methylene chloride/ammonium hydroxide 2/97/1	C ₂₂ H ₂₄ N ₂ O ₂ 0.75 H ₂ O: Calc: C, 73.00; H, 7.10; N, 7.74. Found: C, 73.08; H, 7.12; N, 7.56.
202		4-(chloromethyl)-2-methylthiazole hydrochloride	silica gel, methanol/methylene chloride/ammonium hydroxide 2/97/1	C ₁₇ H ₂₂ N ₂ O ₂ 0.30 H ₂ O: Calc: C, 63.05; H, 7.03; N, 8.65. Found: C, 63.09; H, 7.12; N, 8.63.
203		4-bromobenzyl bromide	80% ethyl acetate/hexane/trace triethylamine	C ₁₉ H ₂₂ NO ₂ Br 0.25 H ₂ O: Calc: C, 59.92; H, 5.96; N, 3.68. Found: C, 59.92; H, 5.76; N, 3.68.
204		2,6-dichlorobenzyl bromide	5% methanol/ethyl acetate/trace triethylamine	C ₁₉ H ₂₁ NO ₂ Cl ₂ : Calc: C, 62.30; H, 5.78; N, 3.82. Found: C, 61.99; H, 5.57; N, 3.79.
205		4-Fluorobenzyl chloride	5% methanol/ethyl acetate/trace triethylamine	C ₁₉ H ₂₂ NO ₂ F 0.10 H ₂ O: Calc: C, 71.74; H, 7.07; N, 4.40. Found: C, 71.70; H, 7.01; N, 4.35.

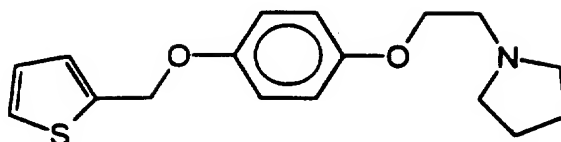
-165-

Ex. No.	Compound	Ar' Precursor	Chrom.	Analysis
206		3-Chlorobenzyl chloride	silica gel, 70% ethyl acetate/hexane/trace triethylamine	$C_{19}H_{22}NO_2Cl$ Calc: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.57; H, 6.60; N, 4.15.
207		2-Fluorobenzyl chloride	5% methanol/ethyl acetate/trace triethylamine	$C_{19}H_{22}NO_2F \cdot 0.60 H_2O$ Calc: C, 69.96; H, 7.17; N, 4.29. Found: C, 69.98; H, 6.97; N, 4.23.
208		2-Chlorobenzyl chloride	5% methanol/ethyl acetate/trace triethylamine	$C_{19}H_{22}NO_2Cl \cdot 0.25 H_2O$ Calc: C, 67.85; H, 6.74; N, 4.16. Found: C, 67.98; H, 6.68; N, 4.16.
209		α' -Chloro- α, α -trifluoro- <i>m</i> -xylene	10% methanol/ethyl acetate/trace triethylamine	$C_{20}H_{22}NO_2F_3$ Calc: C, 65.74; H, 6.07; N, 3.83. Found: C, 65.45; H, 6.04; N, 3.56.

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Ex. No.	Compound	Ar ¹ Precursor	Chrom.	Analysis
210		<i>o</i> -bromo- <i>o</i> -xylene	5% methanol/ethyl acetate/ trace triethylamine	C ₂₀ H ₂₆ NO ₂ 0.60 H ₂ O: Calc: C, 74.55; H, 8.20; N, 4.35. Found: C, 74.51; H, 8.18; N, 4.87.
211		3-Fluorobenzyl chloride	ethanol/methylene chloride/ammonium hydroxide 5/94/1	C ₁₉ H ₂₃ NO ₂ 0.20 H ₂ O: Calc: C, 71.54; H, 7.08; N, 4.39. Found: C, 71.63; H, 7.19; N, 4.34.
212		<i>o</i> -chloro- <i>p</i> -xylene	ethanol/methylene chloride/ammonium hydroxide 1/98/1	C ₂₀ H ₂₆ NO ₂ 0.15 H ₂ O: Calc: C, 76.47; H, 8.12; N, 4.46. Found: C, 76.48; H, 8.22; N, 4.38.
213		4-Methoxybenzyl chloride	ethanol/methylene chloride/ammonium hydroxide 2.5/97/0.5)	C ₂₀ H ₂₆ NO ₂ 0.85 H ₂ O: Calc: C, 70.09; H, 7.85; N, 4.09. Found: C, 70.07; H, 7.47; N, 4.04.
214		1-(chloromethyl)-naphthalene	ethanol/methylene chloride/ammonium hydroxide 5/94/1)	C ₂₃ H ₂₈ NO ₂ 0.15 H ₂ O: Calc: C, 78.89; H, 7.28; N, 4.00. Found: C, 78.89; H, 7.37; N, 3.90.

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Example 215

2-Thiophenemethanol (4.18g, 36.6 mmol), tosyl chloride (7.09g, 37.2 mmol) and pyridine (3 mL, 37.1 mmol) were stirred in 100 mL methylene chloride at RT for 12 hours. The reaction was poured into 200 mL water. The phases were separated, and the organic phase was washed with 2 X 200 mL 10% HCl, 2 X 200 mL water, and dried (Na_2SO_4). The resultant crude tosylate (1.05g, 3.9 mmol) was reacted with the phenol from Example 199 (0.34g, 1.7mmol) and sodium hydride (0.11g, 2.8 mmol, 60% dispersion in mineral oil) in 25 mL DMF at RT overnight. The reaction was poured into 100 mL water and washed with 4 X 50 mL ethyl acetate. The organic phases were dried (Na_2SO_4) and concentrated to afford an amber oil. The crude product was chromatographed (silica gel, ethanol/methylene chloride/ammonium hydroxide 5/94/1) to give an amber oil. The product had the following properties:

Analysis calculated for $\text{C}_{17}\text{H}_{21}\text{NO}_2\text{S} \cdot 0.15 \text{ H}_2\text{O}$:

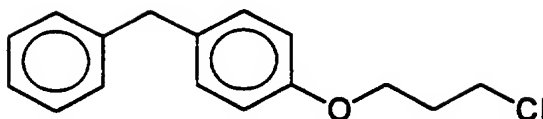
Calc: C, 66.70; H, 7.01; N, 4.58.

Found: C, 66.72; H, 6.94; N, 4.47.

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Example 216

5

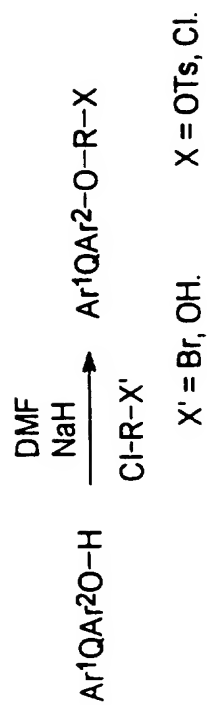


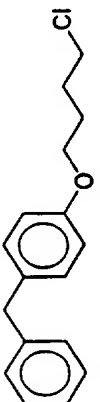
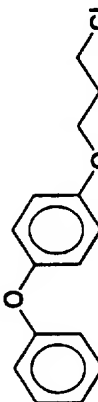
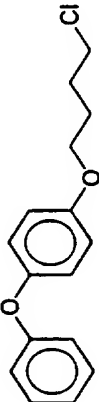
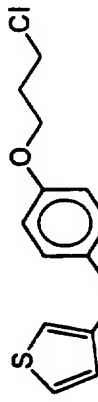
4-Hydroxydiphenyl methane (Aldrich) 1.84 g in 50 ml dimethylformamide (DMF) was added sodium hydride (60% dispersion in mineral oil) 0.5 g (Aldrich) portionwise at R.T. during 15 min. The reaction mixture was stirred for 1/2 hr and 1.57 g of 1-bromo-3-chloro propane (Aldrich) in 10 ml of DMF was added dropwise during 10 min and the mixture was stirred at room temperature overnight.

Diethyl ether 100 ml and 3 ml of water was added to the reaction mixture and the organic phase was further washed with H₂O (10 ml x 2), dried, filtered, the solvent removed in vacuo, and the organic material was chromatographed over silica gel using 5% EtOAc in hexane and gave the title compound as colorless thick oil 2.1 g.

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TABLE 14



Ex. No.	Compound	Starting Phenol	Analysis
217		4-hydroxydiphenyl methane	¹ H NMR: 400 MHz Compound was fully characterized in the next step. See Example No. 226.
218		4-phenoxyphenol	¹ H NMR: 300 MHz Compound was fully characterized in the next step. See Example No. 250.
219		4-phenoxyphenol	¹ H NMR: 300 MHz
220		Ex. 19	M ⁺ = 266.

5

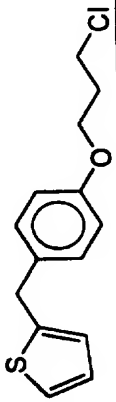
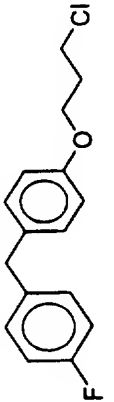
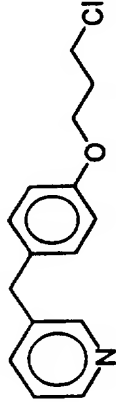
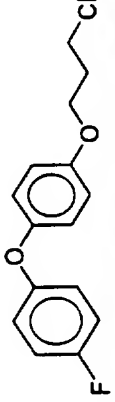
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Ex. No.	Compound	Starting Phenol	Analysis
221		Ex. 18	Compound was fully characterized in the next step. See Example No. 327.
222		Ex. 25	$M^+ = 278$.
223		Ex. 24	$M^+ = 261$.
224		Ex. 41	NMR spectrum consistent with proposed structure.

5

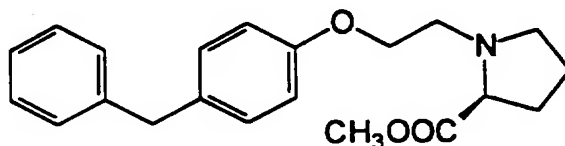
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Example 225 (Method A)

Methyl 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-2S-pyrrolidine-2-carboxylate, monohydrochloride, hydrate

H₂OHCl⁻

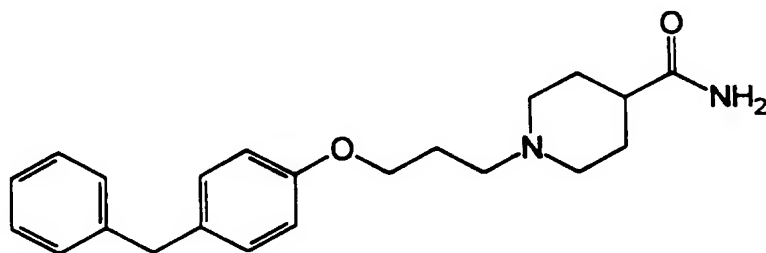
To a stirred solution of 165 mg of L-proline methyl ester hydrochloride in 5 ml of N,N-dimethylformamide was added 500 mg of powdered potassium carbonate and the mixture was stirred under a nitrogen atmosphere at room temperature for 10 minutes. 382 mg of the compound of example 186 was added to the mixture and was heated to 65° and stirred under a nitrogen atmosphere for 4 hrs. The mixture was cooled to room temperature and the solvent was removed by evaporation under reduced pressure to give crude oily gum, which was extracted with ethyl acetate and was washed with water, dried over sodium sulfate and concentrated *in vacuo* to give crude product which was chromatographed on silica using 75% toluene, 25% ethyl acetate as mobile phase to yield 180 mg of oily gum which was converted into its HCl salt using 6 N HCl: Dioxane and crystallization from ether gave 158 mg of the title compound as white crystalline solid.

Analysis Calculated for C₂₁H₂₅NO₃HCl H₂O:

Calculated: C, 64.03; H, 7.16; N, 3.56.

Found: C, 63.76; H, 7.14; N, 3.51.

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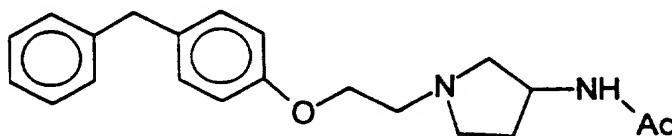
Example 226 (Method B)Preparation of 1-[3-[4-(phenylmethyl)phenoxy]propyl]-4-piperidinecarboxamide+0.25 H₂O

To a stirred solution of 260.5 mg of the compound of example 216 in 5 ml of N,N-dimethylformamide was added 300 mg of powdered K₂CO₃, and was stirred under nitrogen atmosphere for 10 minutes. 150 mg of isonipecotamide was added to the mixture and it was heated to 65°C and was stirred at 65°C under nitrogen atmosphere for 4 hours. The mixture was cooled to room temperature and solvent was removed by evaporation under reduced pressure to give crude oily gum which was dissolved in ethyl acetate and was washed with water, dried over sodium sulfate and concentrated in vacuo to give crude product, which upon crystallization from diethyl ether gave the title compound.

Analysis Calculated C₂₂H₂₈N₂O₂·1/4 H₂O:

Calculated: C, 74.02; H, 8.05; N, 7.85

Found: C, 73.98; H, 8.19; N, 7.72

Example 227 (Method C)

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To a stirred suspension of 3-acetamido pyrrolidine (260 mg,) and potassium carbonate (700 mg, finely divided) in DMF (15 ml), Tosylate of example 186 (700 mg) was added. The reaction mixture was heated at 60°C for 10 hours, evaporated and the residue partitioned between ethyl acetate and sat potassium carbonate solution. The ethyl acetate layer was separated, dried (Na₂SO₄) and evaporated to afford a yellow oil that was further purified by radial chromatography on silica (eluant; methylene chloride/ethanol, 97/3) to yield a clear oil (400mg).

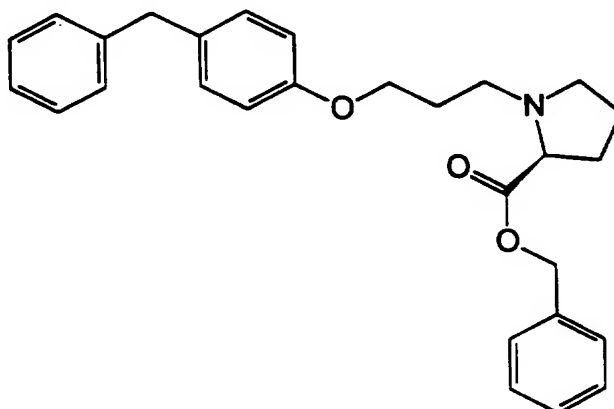
The resulting oil was further purified by crystallization as its HCl salt (ethanol/diethyl ether) to afford the title compound (400 mg).

Analysis Calculated for C₂₁H₂₆N₂O₂ .1HCl:

Calculated: C, 67.28; H, 7.26; N, 7.47.

Found: C, 67.47; H, 7.97; N, 6.88.

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Example 228 (Method D)Phenylmethyl 1-[3-[4-(phenylmethyl)phenoxy]-
propyl]-L-prolinate

To product of example 216 (0.27 g) and 240 mg L-proline benzyl ester hydrochloride in 5 ml DMF was added powdered K_2CO_3 , 280 mg, sodium iodide 50 mg. The reaction mixture was heated at 80° overnight under nitrogen.

It was then cooled to room temperature and 50 ml of ether and 3 ml of water were added. The organic phase was further washed with water (10 ml x 2) and dried. It was filtered and solvent was removed under vacuo. The residue was chromatographed over silica gel using 10:90:1 EtOAc: hexane: Et_3N to give the title compound as colorless oil. 0.32 g was obtained.

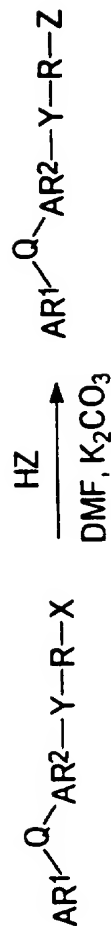
Analysis for $C_{28}H_{31}NO_3$:

Calculated: C, 78.29; H, 7.27; N, 3.26.

Found: C, 78.42; H, 7.15; N, 3.10.

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REACTION



60°
X = OTs, Cl or Br

TABLE 15

Ex. No.	AR ¹ Q AR ² Y R Z	ZH	Method/Prep	Isol'n/Chrom.	Analysis
229			A	A	C ₁₉ H ₂₄ N ₂ O ₂ S · 0.3 H ₂ O Calc: C, 65.22; H, 7.09; N, 8.01. Found: C, 65.30; H, 6.99; N, 7.92.
230			A	A	C ₁₉ H ₂₄ N ₂ O ₂ S Calc: C, 66.25; H, 7.02; N, 8.13. Found: C, 65.91; H, 7.04; N, 8.03.
231			A	A	C ₁₈ H ₂₃ N ₂ O ₂ S · 1.2 H ₂ O Calc: C, 58.90; H, 6.97; N, 11.45. Found: C, 58.78; H, 6.87; N, 11.38. M ⁺ = 345
232			A	A	C ₂₂ H ₂₈ N ₂ O ₃ · 0.3 H ₂ O Calc: C, 70.68; H, 7.71; N, 7.49. Found: C, 70.70; H, 7.16; N, 7.34.

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Ex. No.	AR' Q AR ² Y R Z	ZH	Method/ Prep	Isol'n/ Chrom.	Analysis
233			A	A	C ₂₁ H ₂₆ FN ₂ O ₂ ; Calc: C, 70.76; H, 7.07; N, 7.86. Found: C, 70.52; H, 6.96; N, 7.66. M ⁺ = 356.
234			A	A	C ₂₁ H ₂₆ ClN ₂ O ₂ 0.2H ₂ O; Calc: C, 66.99; H, 6.80; N, 7.44. Found: C, 66.77; H, 6.61; N, 7.33. M ⁺ = 372.
235			A	A	C ₂₁ H ₂₆ FN ₂ O ₂ 0.2H ₂ O; Calc: C, 70.06; H, 7.11; N, 7.78. Found: C, 70.17; H, 7.35; N, 7.78. M ⁺ = 356.
236			A	A	C ₂₀ H ₂₆ N ₃ O ₂ 0.2H ₂ O; Calc: C, 70.03; H, 7.46; N, 12.25. Found: C, 69.82; H, 7.43; N, 12.18. M ⁺ = 339.
237			A	B	C ₂₁ H ₂₆ NO ₃ HCl H ₂ O; Calc: C, 64.03; H, 7.16; N, 3.56. Found: C, 63.76; H, 7.14; N, 3.51.
238			A	B	C ₂₂ H ₂₈ N ₂ O ₂ ; Calc: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.66; H, 7.66; N, 7.82.

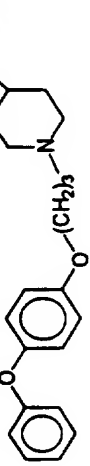
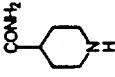
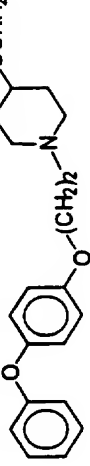
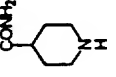
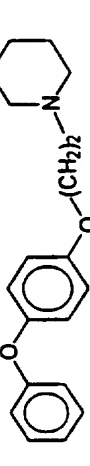
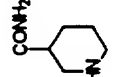
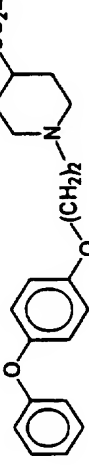
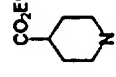
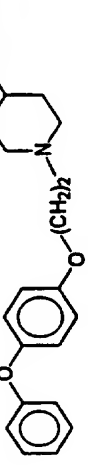
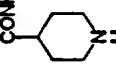
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Ex. No.	AR ¹ Q AR ² Y R Z	ZH	Method/ Prep	Isol'n/ Chrom.	Analysis
239			A	B	C ₂₁ H ₂₈ N ₂ O ₂ ; Calc: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.18; H, 7.88; N, 8.25.
240			A	B	C ₂₁ H ₂₇ NOHCl; Calc: C, 72.91; H, 8.16; N, 4.05. Found: C, 72.60; H, 8.30; N, 4.07.
241			A	B	C ₂₀ H ₂₆ NOHCl; Calc: C, 72.38; H, 7.98; N, 4.22. Found: C, 72.31; H, 7.94; N, 4.17.
242			B	C	C ₂₂ H ₂₈ N ₂ O ₂ ·1/4 H ₂ O; Calc: C, 74.02; H, 8.05; N, 7.85. Found: C, 73.98; H, 8.19; N, 7.72.
243			A	B	C ₂₁ H ₂₈ N ₂ O ₂ ; Calc: C, 73.74; H, 7.78; N, 8.19. Found: C, 73.91; H, 7.87; N, 8.16.
244			B	C	C ₂₂ H ₂₈ N ₂ O ₂ ; Calc: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.66; H, 8.41; N, 7.89.

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Ex. No.	AR ¹ Q AR ² Y R Z	ZH	Method/ Prep	Isol'n/ Chrom.	Analysis
245			A	B	C ₂₃ H ₂₈ NO ₃ ·HCl: Calc: C, 68.39; H, 7.49; N, 3.47. Found: C, 68.20; H, 7.56; N, 3.49.
246			A	B	C ₂₂ H ₂₇ NO ₃ ·HCl: Calc: C, 67.77; H, 7.25; N, 3.59. Found: C, 67.52; H, 7.20; N, 3.55.
247			A	B	C ₂₀ H ₂₆ NO ₂ ·HCl: Calc: C, 69.05; H, 7.53; N, 4.03. Found: C, 68.97; H, 7.47; N, 3.96.
248			A	B	C ₂₈ H ₃₀ N ₂ O ₃ ·1/4H ₂ O: Calc: C, 75.87; H, 6.70; N, 6.10. Found: C, 75.83; H, 6.99; N, 6.14.
249		Ex. 482	A	B	C ₂₈ H ₃₀ N ₂ O ₄ ·1/4H ₂ O: Calc: C, 70.48; H, 7.85; N, 6.32. Found: C, 70.39; H, 7.81; N, 6.25.
250			A	B	C ₂₁ H ₂₈ N ₂ O ₃ : Calc: C, 71.16; H, 7.39; N, 7.9. Found: C, 70.86; H, 7.65; N, 7.73.

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Ex. No.	AR ¹ Q AR ² Y R Z	ZH	Method/ Prep	Isol'n/ Chrom.	Analysis
251			B	C	C ₂₂ H ₂₈ N ₂ O ₂ : Calc: C, 74.97; H, 8.01; N, 7.95 Found: C, 74.66; H, 8.41; N, 7.89
252			B	C	C ₂₀ H ₂₄ N ₂ O ₃ : Calc: C, 70.57; H, 7.11; N, 8.23 Found: C, 70.40; H, 6.93; N, 8.17
253			B	C	C ₂₀ H ₂₄ N ₂ O ₃ · 1/4H ₂ O: Calc: C, 69.64; H, 7.16; N, 8.12 Found: C, 69.53; H, 7.29; N, 7.95
254			B	C	C ₂₂ H ₂₇ NO ₄ · HCl: Calc: C, 65.10; H, 6.95; N, 3.45 Found: C, 64.78; H, 6.64; N, 3.42
255			B	C	C ₂₁ H ₂₆ N ₂ O ₃ : Calc: C, 71.16; H, 7.39; N, 7.90 Found: C, 70.88; H, 7.69; N, 7.87

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Ex. No.	AR ¹ Q AR ² Y R Z	ZH	Method/ Prep	Isol'n/ Chrom.	Analysis
256			C	D	C ₂₁ H ₂₈ N ₂ O ₂ · 1 HCl: Calc: C, 67.28; H, 7.26; N, 7.47. Found: C, 67.47; H, 7.97; N, 6.88.
257			C	D	C ₁₈ H ₂₃ NO ₂ · 1 HCl, 0.25 H ₂ O: Calc: C, 67.45; H, 7.30; N, 4.14. Found: C, 67.42; H, 7.28; N, 4.05.
258			D	E	C ₂₈ H ₃₁ NO ₃ : Calc: C, 78.29; H, 7.27; N, 3.26 Found: C, 78.42; H, 7.15; N, 3.10
259			D	F	C ₂₀ H ₂₅ NO: Calc: C, 81.31; H, 8.53; N, 4.74 Found: C, 81.33; H, 8.84; N, 4.57
260			D	G	C ₂₈ H ₃₂ NO ₃ · 0.2 H ₂ O: Calc: C, 75.42; H, 8.20; N, 3.52 Found: C, 75.12; H, 8.49; N, 3.44
261			D	E	C ₂₉ H ₃₈ NO ₃ : Calc: C, 77.58; H, 7.01; N, 3.48 Found: C, 77.26; H, 7.23; N, 3.46

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Ex. No.	AR ¹ Q AR ² Y R Z	ZH	Method/ Prep	Isol'n/ Chrom.	Analysis
262			D	H	C ₂₃ H ₂₇ NO ₄ : Calc: C, 72.42; H, 7.13; N, 3.67 Found: C, 71.95; H, 6.86; N, 4.16
263			D	I	C ₂₈ H ₃₆ NO ₃ : Calc: C, 76.25; H, 8.61; N, 3.42 Found: C, 76.04; H, 8.76; N, 3.37
264			D	F	C ₂₀ H ₂₆ NO ₃ : Calc: C, 73.37; H, 7.70; N, 4.28 Found: C, 73.33; H, 7.83; N, 4.25
265			D	J	C ₂₁ H ₂₇ NO ₃ ·0.2H ₂ O: Calc: C, 73.10; H, 8.00; N, 4.06 Found: C, 72.91; H, 7.97; N, 4.20
266			D	I	C ₂₈ H ₂₇ NO ₃ ·0.2H ₂ O: Calc: C, 76.39; H, 7.03; N, 3.56 Found: C, 76.10; H, 7.05; N, 3.48
267			D	J	C ₂₀ H ₂₆ NO ₃ ·0.2H ₂ O: Calc: C, 72.57; H, 7.73; N, 4.23 Found: C, 72.67; H, 7.73; N, 4.19

Ex. No.	AR' Q AR ² Y R Z	ZH	Method/ Prep	Isol'n/ Chrom.	Analysis
268			D	A	C ₂₃ H ₃₁ NO ₃ ·0.3H ₂ O; Calc: C, 73.69; H, 8.50; N, 3.74 Found: C, 73.62; H, 8.61; N, 3.70
269			D	E	C ₂₄ H ₃₁ NO ₃ ; Calc: C, 75.56; H, 8.19; N, 3.67 Found: C, 75.32; H, 8.38; N, 3.63
270			D	E	C ₂₃ H ₂₉ NO ₃ ·0.1H ₂ O; Calc: C, 74.81; H, 7.97; N, 3.79 Found: C, 74.60; H, 8.00; N, 3.77
271			B	E	C ₂₄ H ₃₁ N ₃ O ₅ , M ⁺ 448 from Mass spectrometry NMR consistent with the structure.
272			D	E	C ₂₃ H ₂₉ NO ₃ ; Calc: C, 74.33; H, 8.22; N, 3.94 Found: C, 74.21; H, 8.23; N, 3.86
273			D	E	C ₂₃ H ₃₁ NO ₃ ·0.2H ₂ O; Calc: C, 77.70; H, 7.51; N, 3.33 Found: C, 76.47; H, 7.77; N, 3.16
274			D	F	C ₂₃ H ₃₁ NO ₃ ·0.1H ₂ O; Calc: C, 74.40; H, 8.47; N, 3.77 Found: C, 74.19; H, 8.55; N, 3.72

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Ex. No.	AR ¹ Q AR ² Y R Z	ZH	Method/ Prep	Isol'n/ Chrom.	Analysis
275		Ex. 479	B	L	C ₂₂ H ₂₂ NO ₃ ·0.50 H ₂ O: Calc: C, 72.90; H, 7.79; N, 3.86. Found: C, 72.97; H, 7.95; N, 3.92.
276		Ex. 481	B	M	¹ H NMR (CDCl ₃) δ 2.12 (2H, q), 2.61 (1H, q), 2.71-2.97 (4H, m), 3.04 (2H, m), 3.69 (3H, s), 3.92 (2H, s), 4.06 (2H, t), 6.83 (2H, d), 7.09 (2H, d), 7.18 (3H, m), 7.27 (2H, t); HRMS, m/z 339.1831 (calc'd for C ₂₁ H ₂₆ NO ₃ , 339.1834).
277			B	N	C ₂₁ H ₂₆ N·HCl·0.25 H ₂ O: Calc: C, 75.88; H, 8.04; N, 4.21; Cl, 10.67. Found: C, 76.06; H, 8.28; N, 4.29; Cl, 10.53.
278		Ex. 474	B	N	C ₂₁ H ₂₆ N·HCl·0.30 H ₂ O: Calc: C, 75.88; H, 8.04; N, 4.20; Cl, 10.64. Found: C, 75.88; H, 8.19; N, 4.28; Cl, 10.35.
279		Ex. 443	B	N	C ₂₁ H ₂₆ N ₂ O ₂ ·1.1 HCl·0.1 H ₂ O: Calc: C, 66.31; H, 7.23; N, 7.37; Cl, 10.25. Found: C, 66.17; H, 7.51; N, 7.31; Cl, 10.21.
280			B	N	C ₂₀ H ₂₂ NO ₂ ·1.1 HCl·0.5 H ₂ O: Calc: C, 69.76; H, 7.36; N, 4.07; Cl, 11.84. Found: C, 69.97; H, 7.38; N, 4.01; Cl, 11.95.
281			B	N	C ₂₂ H ₂₆ N ₂ O ₂ ·0.25 H ₂ O: Calc: C, 74.44; H, 7.53; N, 7.89. Found: C, 74.59; H, 7.41; N, 7.78.

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Ex. No.	AR' Q AR ² Y R Z	ZH	Method/ Prep	Isol'n/ Chrom.	Analysis
282			B	N	C ₂₂ H ₂₈ N ₂ O ₃ · HCl Calc: C, 69.30; H, 7.27; N, 3.37; Cl, 8.52 Found: C, 69.20; H, 7.28; N, 3.27; Cl, 8.81
283		Ex. 474	B	N	C ₂₈ H ₃₂ N ₂ O ₃ · HCl · H ₂ O Calc: C, 67.35; H, 7.23; N, 3.14; Cl, 7.95 Found: C, 67.38; H, 6.86; N, 3.14; Cl, 7.98
284		Ex. 443	B	N	
285			B	N	C ₂₂ H ₂₈ N ₂ O ₂ · HCl · H ₂ O Calc: C, 65.25; H, 7.22; N, 6.92; Cl, 8.76 Found: C, 65.50; H, 7.13; N, 6.61; Cl, 8.87
286			B	N	C ₂₃ H ₂₈ N ₂ O ₂ · 1.25 H ₂ O Calc: C, 71.38; H, 7.94; N, 7.24 Found: C, 71.68; H, 7.81; N, 7.26
287			B	N	C ₁₉ H ₂₂ N ₂ O ₂ · 1.9 HCl · 0.5 H ₂ O Calc: C, 61.23; H, 6.73; N, 7.52; Cl, 18.07 Found: C, 61.60; H, 6.50; N, 7.60; Cl, 18.37
288			B	N	C ₂₁ H ₂₈ N ₂ O ₂ Calc: C, 71.77; H, 7.17; N, 11.96 Found: C, 72.14; H, 7.11; N, 11.98

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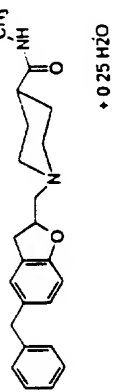
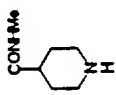
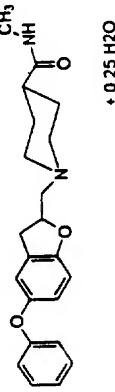
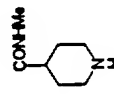
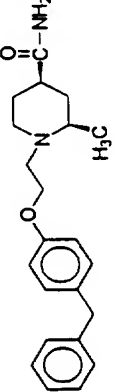
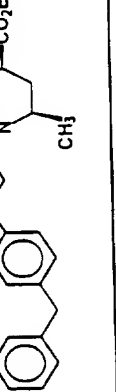
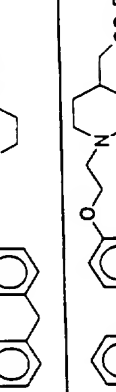
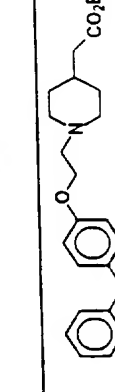
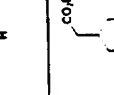


Ex. No.	AR' Q AR ² Y R Z	ZH	Method/ Prep	Isol'n/ Chrom.	Analysis
289			B	N	C ₁₉ H ₂₁ NO ₂ , 1 HCl: Calc: C, 68.77; H, 6.68; N, 4.22; Cl, 10.67 Found: C, 68.32; H, 7.08; N, 4.08; Cl, 10.72
290			B	N	C ₁₉ H ₂₁ NO ₂ , 1 HCl: Calc: C, 71.57; H, 6.86; N, 7.95 Found: C, 71.32; H, 7.20; N, 7.83
291			B	N	C ₂₃ H ₂₉ NO ₄ , 1 HCl: Calc: C, 66.10; H, 6.75; N, 3.35; Cl, 8.48 Found: C, 66.23; H, 7.02; N, 3.25; Cl, 8.43
292			B	N	C ₂₁ H ₂₉ NO, HCl: Calc: C, 73.34; H, 7.62; N, 4.07; Cl, 10.31 Found: C, 73.08; H, 7.98; N, 4.15; Cl, 10.23
293			B	N	C ₂₃ H ₂₉ N ₃ O ₂ , HCl, 0.25 H ₂ O: Calc: C, 68.13; H, 7.33; N, 6.91; Cl, 8.74 Found: C, 68.12; H, 7.23; N, 6.77; Cl, 8.76
294			B	N	C ₂₇ H ₂₉ N ₃ O ₂ , HCl, H ₂ O: Calc: C, 65.25; H, 7.22; N, 6.92; Cl, 8.76 Found: C, 65.50; H, 7.13; N, 6.61; Cl, 8.87

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
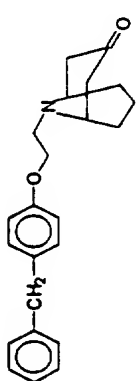

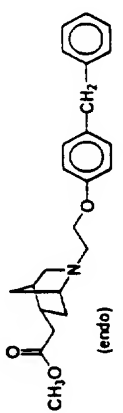
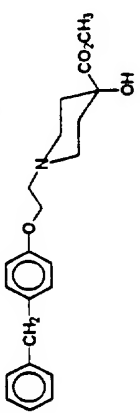
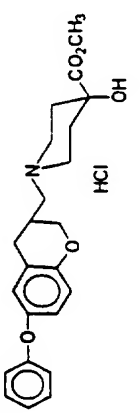
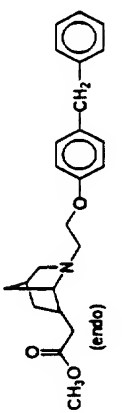
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Ex. No.	AR ¹ Q AR ² Y R Z	ZH	Method/ Prep	Isol'n/ Chrom.	Analysis
295			A	N	C ₂₂ H ₂₆ N ₂ O ₂ · 0.25 H ₂ O Calc: C, 74.87; H, 7.79; N, 7.95 Found: C, 74.49; H, 7.98; N, 7.46
296			A	N	C ₂₂ H ₂₆ N ₂ O ₂ · 0.25 H ₂ O Calc: C, 71.23; H, 7.20; N, 7.55 Found: C, 71.00; H, 7.17; N, 7.47
297		Ex. 468	A	L	C ₂₂ H ₂₆ N ₂ O ₂ · 0.25 H ₂ O Calc: C, 74.02; H, 8.05; N, 7.85 Found: C, 74.29; H, 7.99; N, 7.45
298		Ex. 469	A	A	C ₂₄ H ₃₁ NO ₃ Calc: C, 75.66; H, 8.19; N, 3.67 Found: C, 75.23; H, 7.99; N, 3.65
299		Ex. 470	A	A	C ₂₃ H ₃₀ N ₂ O ₂ · 0.6 H ₂ O Calc: C, 73.22; H, 8.33; N, 7.42 Found: C, 73.05; H, 8.25; N, 7.41
300			A	A	C ₂₃ H ₃₀ NO ₄ · HCl · 0.25 H ₂ O Calc: C, 65.08; H, 7.24; N, 3.30 Found: C, 65.28; H, 7.07; N, 3.53
301			A	A	C ₂₂ H ₃₁ NO ₃ · HCl Calc: C, 68.97; H, 7.72; N, 3.35 Found: C, 69.52; H, 7.81; N, 3.46

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Ex. No.	AR ¹ Q AR ² Y R Z	ZH	Method/ Prep	Isol'n/ Chrom.	Analysis
302			B	A	C ₂₄ H ₃₃ NO ₅ · HCl 0.25 H ₂ O; Calc: C, 68.79; H, 7.97; N, 3.21. Found: C, 69.00; H, 8.12; N, 3.26.
303			A	K	C ₂₃ H ₂₇ NO ₅ ; Calc: C, 79.05; H, 7.79; N, 4.01. Found: C, 78.80; H, 7.61; N, 3.98.
304		Ex. 489	A	K	C ₂₄ H ₃₃ NO ₅ ; Calc: C, 75.96; H, 7.70; N, 3.69. Found: C, 75.68; H, 8.08; N, 3.63.
305		Ex. 494	A	K	C ₂₂ H ₂₇ NO ₅ ; Calc: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.44; H, 7.66; N, 3.77.
306		Ex. 494	B	K	C ₂₂ H ₂₇ NO ₅ · HCl · 0.25 H ₂ O; Calc: C, 62.26; H, 6.29; N, 3.30; Cl, 8.35. Found: C, 62.00; H, 6.44; N, 3.23; Cl, 8.66.
307		Ex. 492	A	K	C ₂₄ H ₃₃ NO ₅ ; Calc: C, 75.96; H, 7.70; N, 3.69. Found: C, 75.57; H, 7.80; N, 3.68.

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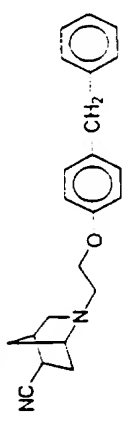
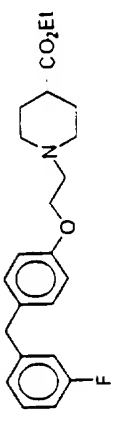
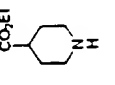
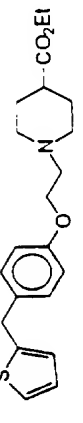

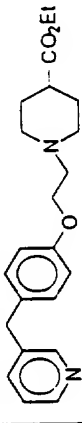

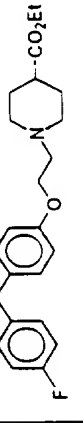

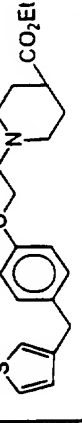

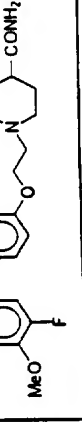

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Ex. No.	AR ¹ Q AR ² Y R Z	ZH	Method/ Prep	Isol'n/ Chrom.	Analysis
308		Ex. 506	A	K	¹ H NMR 300 MHz Compound was fully characterized in the next step. See Example No. 440.
309			A	A	C ₂₃ H ₂₈ O ₃ NF Calc: C, 71.66; H, 7.32; N, 3.63. Found: C, 71.63; H, 7.58; N, 3.65. M ⁺ = 385
310			A	A	C ₂₁ H ₂₇ SN O ₃ Calc: C, 67.53; H, 7.29; N, 3.75. Found: C, 67.47; H, 7.35; N, 3.62. M ⁺ = 373
311			A	A	C ₂₃ H ₂₈ O ₃ N ₂ 0.25 H ₂ O Calc: C, 70.85; H, 7.70; N, 7.51. Found: C, 70.86; H, 7.59; N, 7.13. M ⁺ = 368
312			A	A	C ₂₃ H ₂₈ NFO ₃ 0.1 H ₂ O Calc: C, 71.33; H, 7.34; N, 3.62. Found: C, 71.19; H, 7.34; N, 3.52. M ⁺ = 386
313			A	A	C ₂₁ H ₂₇ SN O ₃ Calc: C, 67.53; H, 7.29; N, 3.75. Found: C, 67.22; H, 7.05; N, 3.65. M ⁺ = 373
314			A	A	C ₂₂ H ₂₇ N ₂ O ₃ F 0.3 H ₂ O Calc: C, 67.43; H, 7.10; N, 7.15. Found: C, 67.41; H, 7.23; N, 7.07. M ⁺ = 386

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Ex. No.	AR' Q AR' Y R Z	ZH	Method/ Prep	Isol'n/ Chrom.	Analysis
315		Ex. 512	A	A	C ₂₄ H ₂₃ N ₂ O ₂ ; Calc: C, 75.25; H, 8.48; N, 7.36. Found: C, 75.41; H, 8.48; N, 7.18.
316		Ex. 508	A	A	C ₂₃ H ₂₀ N ₂ O ₂ · 0.5 H ₂ O; Calc: C, 73.57; H, 8.32; N, 7.46. Found: C, 73.30; H, 8.02; N, 7.31.
317		Ex. 510	A	A	C ₂₄ H ₂₃ NO ₃ · 1HCl · 0.5 H ₂ O; Calc: C, 67.51; H, 7.79; N, 3.28. Found: C, 67.54; H, 7.72; N, 3.17.
318			D	F	C ₁₈ H ₂₃ NO ₃ ; Calc: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.56; H, 7.79; N, 4.38.
319			D	F	C ₂₄ H ₂₈ NO ₃ ; Calc: C, 76.78; H, 6.71; N, 3.73. Found: C, 76.38; H, 6.34; N, 3.77.
320			D	F	C ₂₁ H ₂₃ NO ₃ ; Calc: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.71; H, 8.21; N, 4.01.

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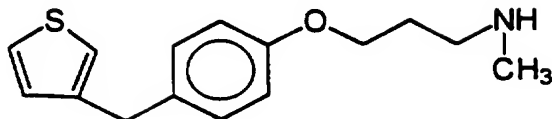
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Ex. No.	AR' Q AR' Y R Z	ZH	Method/ Prep	Isol'n/ Chrom.	Analysis
321			A	G	$C_{22}H_{29}NO_3 \cdot 0.5 H_2O$ Calc: C, 72.50; H, 8.30; N, 3.84. Found: C, 72.46; H, 8.14; N, 3.80.
322			A	G	$C_{27}H_{31}NO_3 \cdot 0.2 H_2O$ Calc: C, 77.00; H, 7.51; N, 3.33. Found: C, 76.47; H, 7.77; N, 3.16.
323			A	G	$C_{22}H_{27}N_2O_3 \cdot 0.3 H_2O$ Calc: C, 67.43; H, 7.10; N, 7.15. Found: C, 67.41; H, 7.23; N, 7.07.
324			A	G	$C_{19}H_{23}NO_3$ Calc: C, 72.82; H, 7.40; N, 4.47. Found: C, 73.04; H, 7.64; N, 4.45.
325		Ex. 486	A	A	$C_{27}H_{31}NO_3 \cdot HCl$ Calc: C, 68.73; H, 7.02; N, 3.48. Found: C, 68.88; H, 7.16; N, 3.39.

ISOLATION/PURIFICATION PROCEDURES

- A. 84/15/1 $CHCl_3$ /EtOH/NH₄OH
 B. 75/25 Toluene/Ethyl Acetate
 C. Crystallization from Et₂O
 D. 97/3 Methylene Chloride/Ethanol
 E. 10/90/1 EtOAc:Hexane:NEt₃
 F. 99/1 EtOAc/NEt₃
 G. 20/80/1 EtOAc/Toluene/TEA
 H. 1/1 EtOAc/Heptane
 I. 50:50:1 EtOAc/Toluene/TEA
 J. 10:1:1 EtOH/EtOAc/TEA
 K. 1/98 5/0.5 MeOH/CH₂Cl₂/NH₄OH
 L. 3/97/trace EtOH/EtOAc/NH₄OH
 M. 100:0:0.5 CH₂Cl₂/MeOH/NH₄OH
 N. 85/14/1 $CHCl_3$ /EtOH/NH₄OH

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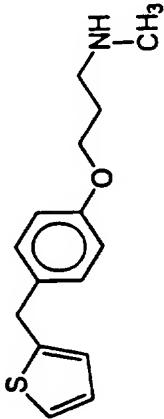
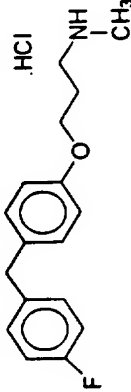
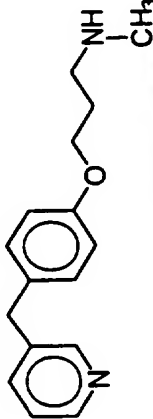
Example 326

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To a stirred solution of methylamine (40% solution in H₂O, Aldrich) (13.7 mL, 180 mmol) was added a solution of example 220 (0.47 g, 1.8 mmol, in CH₃CN 5 mL). The
10 resulting mixture was heated to 45-50°C for 4-5 hours and then allowed to stir at r.t. for 15 hours. The reaction was concentrated in vacuo and the aqueous residue extracted with EtOAc (2 x 15 mL). The organic
15 layers were combined and acidified with 1N HCl to PH 1 at 0°C. A white precipitate was formed, and the solid was collected by vacuum filtration. The solid was washed with 1N HCl, followed by hexane to afford 0.35 g salt. The solid was dissolved in 10% NaOH (30 mL) and
20 extracted with Et₂O (2 x 20 mL). The organic layers were combined, dried over Na₂SO₄, and concentrated in vacuo to give the free amine as a clear colorless oil (0.3 g). The resulting product was fully characterized in the next step. See Example No. 330.

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TABLE 16

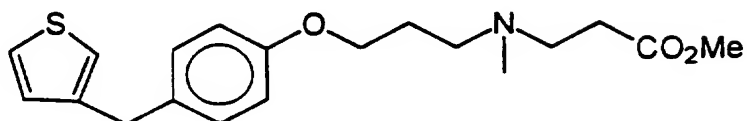
Ex. No.	Compound	Starting Material	Analysis
327		Ex. 221	M ⁺ = 261
328		Ex. 222	M ⁺ = 273
329		Ex. 223	M ⁺ = 256

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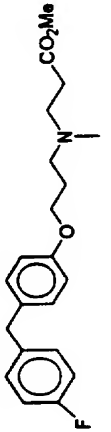
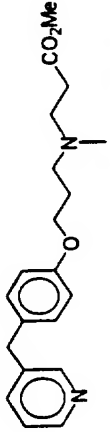
Example 330

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To a stirred solution of example 326 (0.30 g, 1.1 mmol in CH_2Cl_2 (6 mL) was added methyl acrylate (Aldrich, 0.13 mL, 1.5 mmol) at r.t. The reaction was
10 allowed to stir at r.t. for 17 hours, and then concentrated under a stream of nitrogen gas. The residue was purified by column chromatography using 10% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ as eluant to afford 0.32 g of the title compound as a clear colorless oil. The resulting
15 product had the following properties: Analysis calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_3\text{S}$: C, 65.58; H, 7.25; N, 4.03. Found: C, 65.38; H, 7.30; N, 3.95.

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TABLE 17

Ex. No.	Compound	Starting Material	Analysis
331		Ex. 327	$C_{19}H_{26}NO_3 \cdot 0.2 H_2O$ Calc: C, 65.00; H, 7.29; N, 3.99. Found: C, 64.94; H, 7.19; N, 3.90. $M^+ = 347$
332		Ex. 328	$C_{21}H_{26}O_3 \cdot NF \cdot 0.25 H_2O$ Calc: C, 69.30; H, 7.34; N, 3.85. Found: C, 69.26; H, 7.41; N, 3.77. $M^+ = 359$
333		Ex. 329	$C_{20}H_{26}N_2O_3$ Calc: C, 70.15; H, 7.65; N, 8.18. Found: C, 69.82; H, 7.47; N, 7.99. $M^+ = 342$

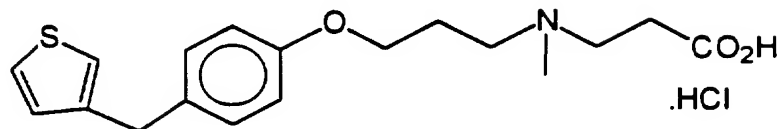
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Example 334

To a stirred solution of example 330 (80 mg, 0.23 mmol) was added 6 N HCl (1 mL). The reaction was
10 heated to 70°C for 4 hours, then concentrated in vacuo to give a white solid. The solid was slurried with Et₂O and collected by vacuum filtration to give 110 mg of the title compound. The resulting product had the following properties: Analysis calcd for C₁₉H₂₄NO₃SCl 1.3
15 H₂O: C, 56.30; H, 6.01; N, 3.46. Found: C, 56.05; H, 6.22; N, 3.37.

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TABLE 18

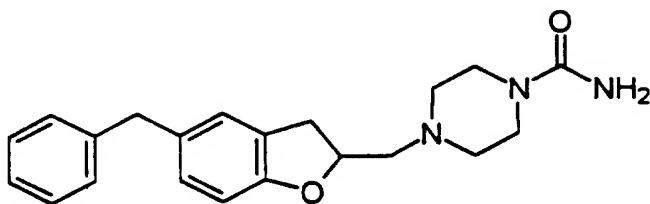
Ex. No.	Compound	Starting Material	Analysis
335		Ex. 331	C ₁₈ H ₂₄ NO ₃ Cl: Calc: C, 58.45; H, 6.54; N, 3.79. Found: C, 58.12; H, 6.30; N, 3.65. M ⁺ = 333
336		Ex. 332	C ₂₀ H ₂₀ FNO ₃ Cl: Calc: C, 62.90; H, 6.60; N, 3.67. Found: C, 62.43; H, 6.72; N, 3.58. M ⁺ = 345

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Example 337+ 0.5 H₂O

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10 A mixture of the product of Example 180 (0.48 g), N-benzylpiperazine (1 mL), K₂CO₃ (0.7 g) in DMF (4 mL) was heated to 80°C for 16 hr. The volatiles were removed in vacuo and the residue was extracted with ethyl acetate and water. The organic phase was washed with
15 water (3 times), dried over MgSO₄ and concentrated. The residue was chromatographed over silica gel using CHCl₃/EtOH/aqueous NH₃ (85/14/1) as eluant to give a N-benzyl piperazine derivative. This product in 30 mL of ethanol was hydrogenated over 20% Pd(OH)₂ on carbon at
20 60 psi hydrogen atmosphere for 18.4 h. The mixture was filtered and the filtrate concentrated. The residue (Sample A) was heated to reflux with toluene (4 mL) and trimethylsilylisocyanate (2.5 mL) for 3h. The mixture was cooled and chromatographed over silica gel
25 using CHCl₃/EtOH/aqueous NH₃ (85/14/1) as eluant to give the title product as a white solid.

Anal. for C₂₁H₂₅N₃O₂. 0.5 H₂O

30	Calculated		Found
	69.98	C	69.78
	7.27	H	6.82
	11.66	N	11.53

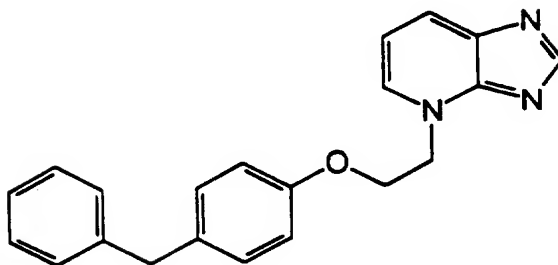
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Example 338 A, B and C

A.

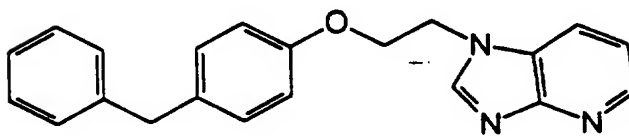
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B.

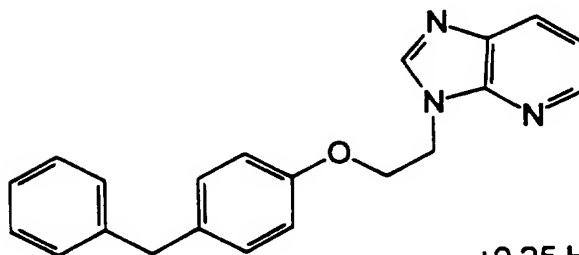
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C.

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+0.25 H₂O

To a stirred solution of 1.5 g of tosylate prepared in example 186 in 20 ml of N,N-dimethylformamide was added 1.5 g of K₂CO₃ and 480 mg of 4-azabenzimidazole. The mixture was heated to 65°C for 4 hours, the mixture was cooled to room temperature and extracted with ethyl acetate. The organic extract was washed with water, dried over Na₂SO₄ and concentrated in vacuo to give crude oily gum which was chromatographed over silica gel to yield the title compounds 338A, 338B and 338C (in order of elution).

A: Calcd for C₂₁H₁₉N₃O · 1/2H₂O:

Calculated: C, 74.53; H, 5.96; N, 12.42

40 Found: C, 74.30; H, 5.81; N, 12.45

B: Calcd for C₂₁H₁₉N₃O:

Calculated: C, 76.57; H, 5.89; N, 12.76

Found: C, 76.48; H, 5.76; N, 12.81

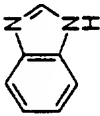
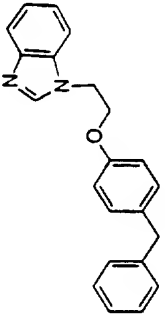
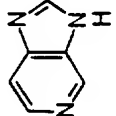
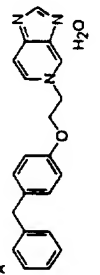
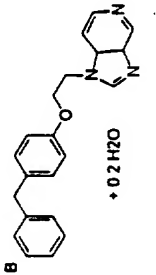
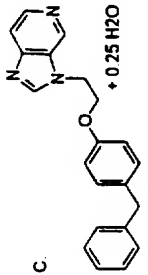
C: Calcd for C₂₁H₁₉N₃O · 1/4H₂O:

45 Calculated: C, 75.54; H, 5.89; N, 12.59

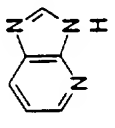
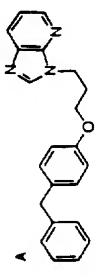
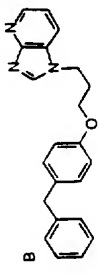

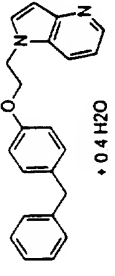
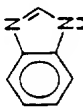
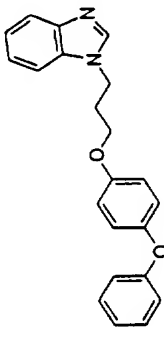
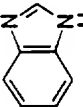
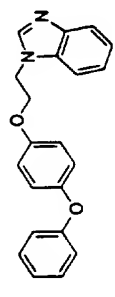
Found: C, 75.80; H, 5.75; N, 12.64

TABLE 19

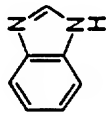
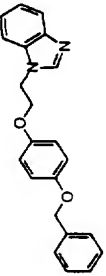
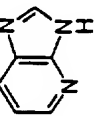
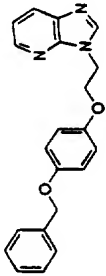
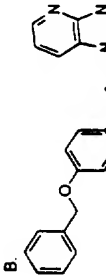
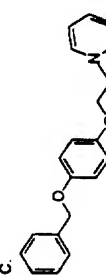


Ex. #	Starting Tosylate or Starting Chloride	ZH	Product	Isolation Chromatography	Analysis
339	Ex. 186			Silica, chloroform/ ethanol/NH ₄ OH; 92.5/7/0.5	C ₂₂ H ₂₀ N ₂ O: Calc: C, 80.46; H, 6.14; N, 8.53 Found: C, 79.90; H, 6.23; N, 8.40
340	Ex. 186		<div style="display: flex; justify-content: space-around;"> <div style="text-align: center;">  A </div> <div style="text-align: center;">  B + 0.2 H₂O </div> <div style="text-align: center;">  C + 0.25 H₂O </div> </div>	Silica, ethanol/ methylene chloride; 10/90	<div style="display: flex; justify-content: space-between;"> <div> C₂₁H₁₈N₂O·H₂O: Calc: C, 72.60; H, 6.09; N, 12.10 Found: C, 72.94; H, 5.68; N, 12.25 </div> <div> C₂₁H₁₈N₂O·2H₂O: Calc: C, 75.74; H, 5.87; N, 12.62 Found: C, 76.03; H, 5.90; N, 12.66 </div> </div> <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div> C₂₁H₁₈N₂O·1/4H₂O: Calc: C, 75.54; H, 5.89; N, 12.59 Found: C, 75.90; H, 5.92; N, 12.60 </div> </div>

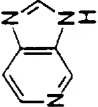
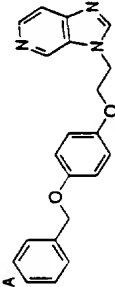
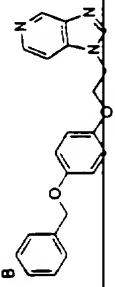
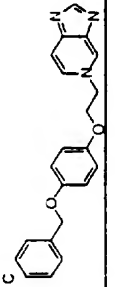
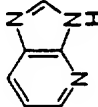
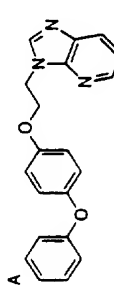
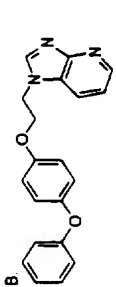
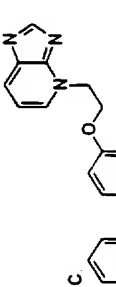
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Ex. #	Starting Tosylate or Starting Chloride	ZH	Product	Isolation Chromatography	Analysis
341	Ex. 216			Silica, methylene chloride/ethanol/ NH ₄ OH, 90/9/1	C ₂₂ H ₂₁ N ₃ O: Calc: C, 76.94; H, 6.16; N, 12.24 Found: C, 76.78; H, 6.35; N, 12.20
					
342	Ex. 186			Silica, 75/25; ethylacetate/toluene	C ₂₂ H ₂₀ N ₂ O·0.4H ₂ O: Calc: C, 78.73; H, 6.25; N, 8.35 Found: C, 78.81; H, 6.33; N, 8.04
343	Ex. 184			silica, methanol/ methylene chloride/ ammonium hydroxide 1/98.5/0.5	C ₂₂ H ₂₀ N ₂ O·0.25 H ₂ O: Calc: C, 75.73; H, 5.92; N, 8.03. Found: C, 75.72; H, 5.95; N, 7.96.
344	Ex. 188			silica gel, methanol/ methylene chloride/ ammonium hydroxide 5/94/1	C ₂₁ H ₁₈ N ₂ O ₂ ·0.15 H ₂ O: Calc: C, 75.73; H, 5.54; N, 8.42. Found: C, 75.77; H, 5.62; N, 8.46.

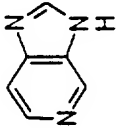
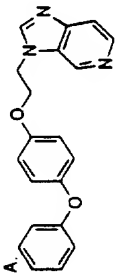
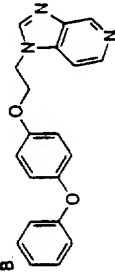
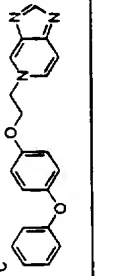
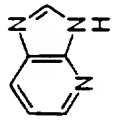
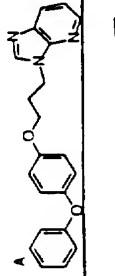
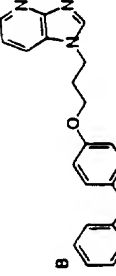
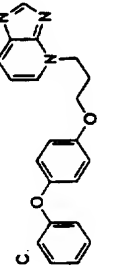
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Ex. #	Starting Tosylate or Starting Chloride	ZH	Product	Isolation Chromatography	Analysis
345	Ex. 189			silica gel, methanol/ methylene chloride/ ammonium hydroxide 1/98.5/0.5.	$C_{22}H_{20}N_2O_2$; Calc: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.44; H, 5.98; N, 8.05.
346	Ex. 189		<div>A </div> <div>B </div> <div>C </div>	silica gel, methanol/ methylene chloride/ ammonium hydroxide 1/98.5/0.5.	$C_{21}H_{19}N_3O_2 \cdot 0.2 H_2O$; Calc: C, 72.27; H, 5.60; N, 12.04. Found: C, 72.34; H, 5.58; N, 11.54. H.R.M.S. M ⁺ calc: 345.1477. Found: 345.1473. $C_{21}H_{19}N_3O_2$; Calc: C, 73.03; H, 5.54; N, 12.17. Found: C, 73.12; H, 5.59; N, 12.15. $C_{21}H_{19}N_3O_2 \cdot 0.20 H_2O$; Calc: C, 72.26; H, 5.60; N, 12.04. Found: C, 72.30; H, 5.62; N, 11.77.


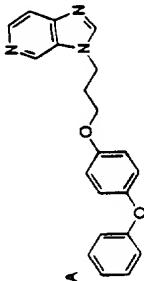
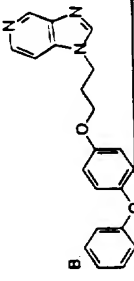
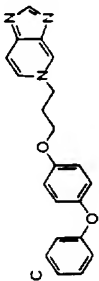

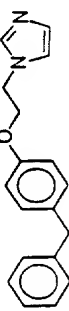
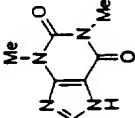
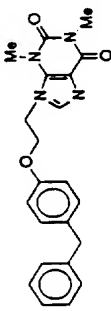
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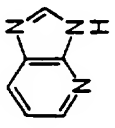
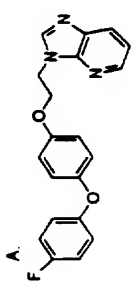
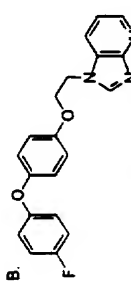
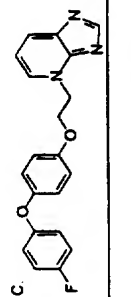
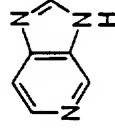
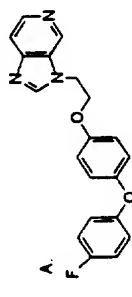
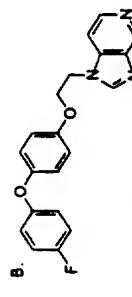
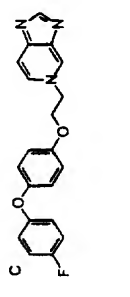
Ex. #	Starting Tosylate or Starting Chloride	ZH	Product	Isolation Chromatography	Analysis
347	Ex. 189		 A	methanol/methylene chloride/ammonium hydroxide 1/98.5/0.5.	$C_{21}H_{18}N_2O_2 \cdot 0.40 H_2O$ Calc: C, 71.53; H, 5.66; N, 11.92. Found: C, 71.71; H, 5.68; N, 11.42. H.R.M.S. M ⁺ calc: 345.1477. Found: 345.1479.
			 B		
			 C		
348	Ex. 188		 A	methanol/methylene chloride/ammonium hydroxide 5/94/1	$C_{20}H_{17}N_2O_2 \cdot 0.25 H_2O$ Calc: C, 71.52; H, 5.25; N, 12.51. Found: C, 71.43; H, 5.17; N, 12.50.
			 B		
			 C		
					$H.R.M.S. M^+$ calc: 331.1321. Found: 331.1296.

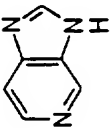
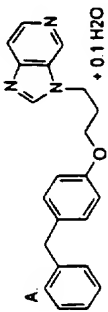
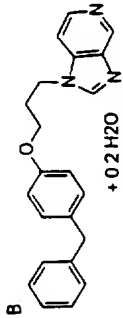
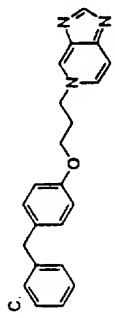
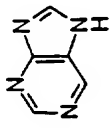
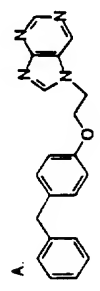
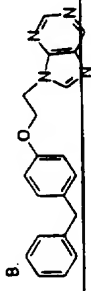
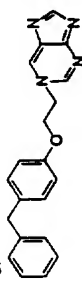
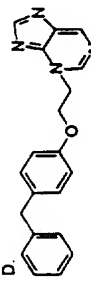
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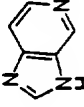
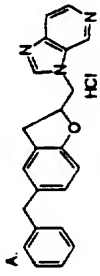
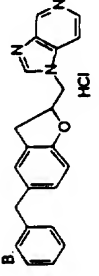
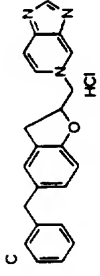
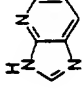
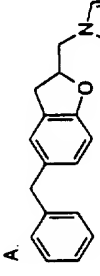
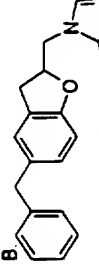
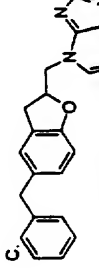
Ex. #	Starting Tosylate or Starting Chloride	ZH	Product	Isolation Chromatography	Analysis
349	Ex. 188			methanol/methylene chloride/ammonium hydroxide 1/98.5/0.5.	$C_{20}H_{17}N_3O_2$; Calc: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.19; H, 5.23; N, 12.61.
					
					
350	Ex. 184			methanol/methylene chloride/ammonium hydroxide 5/94/1.	$C_{21}H_{19}N_3O_2 \cdot 0.15 H_2O$; Calc: C, 72.46; H, 5.59; N, 12.07. Found: C, 72.48; H, 5.65; N, 11.97.
					
					
					H.R.M.S. M ⁺ calc: 345.1478. Found: 345.1493.

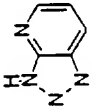
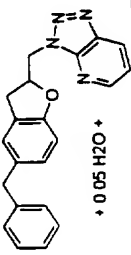
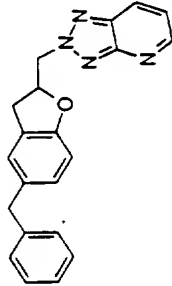
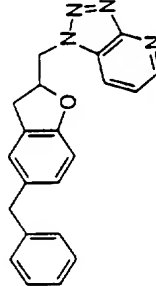

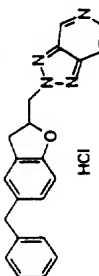
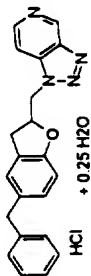
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Ex. #	Starting Tosylate or Starting Chloride	ZH	Product	Isolation Chromatography	Analysis
351	Ex. 184			methanol/methylene chloride/ammonium hydroxide 5/94/1.	$C_{21}H_{19}N_3O_2 \cdot 0.50 H_2O$ Calc: C, 71.17; H, 5.69; N, 11.86. Found: C, 71.16; H, 5.46; N, 11.46.
					
					
352	Ex. 186			Silica, chloroform/ ethanol/ NH_4OH ; 92.5/7/0.5	$C_{19}H_{18}N_2O \cdot HCl$ Calc: C, 68.67; H, 6.08; N, 8.9. Found: C, 68.54; H, 6.07; N, 8.79.
353	Ex. 186			Silica, EtOAc	$C_{23}H_{22}N_4O_3$ Calc: C, 67.35; H, 5.84; N, 14.35. Found: C, 67.68; H, 5.68; N, 14.35.

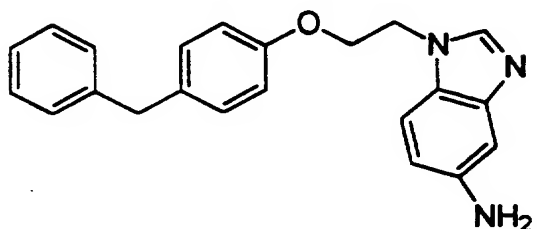
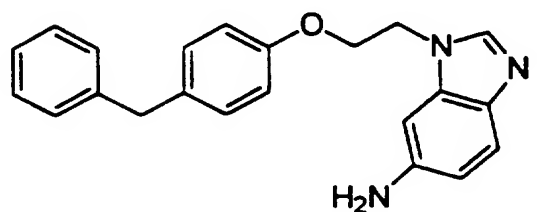
Ex. #	Starting Tosylate or Starting Chloride	ZH	Product	Isolation Chromatography	Analysis
354	Ex. 161			100:1:1 CH ₂ Cl ₂ /MeOH/NH ₄ OH	C ₂₀ H ₁₆ FN ₃ O ₂ ; Calc: C, 68.76; H, 4.62; N, 12.03. Found: C, 68.66; H, 4.63; N, 11.78.
					
					
355	Ex. 161			100:1:1 CH ₂ Cl ₂ /MeOH/NH ₄ OH	C ₂₀ H ₁₆ FN ₃ O ₂ · 0.2 H ₂ O; Calc: C, 68.06; H, 4.68; N, 11.90. Found: C, 68.28; H, 4.72; N, 11.72.
					
					
					HRMS, m/z 349.1222 calc: C ₂₀ H ₁₆ FN ₃ O ₂ , 349.1227.
					HRMS, m/z 349.1244 calc: C ₂₀ H ₁₆ FN ₃ O ₂ , 349.1227.
					mp 126-128 °C.

Ex. #	Starting Tosylate or Starting Chloride	ZH	Product	Isolation Chromatography	Analysis
356	Ex. 216			silica gel, methanol/ methylene chloride/ ammonium hydroxide 5/94.5/0.5.	$C_{22}H_{21}N_3O \cdot 0.1H_2O$ Calc: C, 76.54; H, 6.19; N, 12.17. Found: C, 76.86; H, 6.15; N, 12.10.
					
					
357	Ex. 186			silica gel, methanol/ methylene chloride/ ammonium hydroxide 5/94.5/0.5.	$C_{20}H_{18}N_4O \cdot 0.1H_2O$ Calc: C, 72.31; H, 5.52; N, 16.87. Found: C, 72.22; H, 5.59; N, 16.90.
					
					
					

Ex. #	Starting Tosylate or Starting Chloride	ZH	Product	Isolation Chromatography	Analysis
358	Ex. 180			Ethanol/methylene chloride/aq. NH ₃ 10/90/1	C ₂₂ H ₁₈ N ₃ O. 2HCl. Calc: C, 63.77; H, 5.11; N, 10.14; Cl, 17.11. Found: C, 63.43; H, 5.32; N, 10.11; Cl, 16.95.
					
					
359	Ex. 180			Ethanol/methylene chloride/aq. NH ₃ 10/90/1	C ₂₂ H ₁₈ N ₃ O. HCl. 0.25 H ₂ O Calc: C, 69.10; H, 5.40; N, 10.99; Cl, 9.27. Found: C, 69.11; H, 5.50; N, 11.48; Cl, 9.48.
					
					

Ex. #	Starting Tosylate or Starting Chloride	ZH	Product	Isolation Chromatography	Analysis
360	Ex. 180		 + 0.05 H ₂ O +	Ethylacetate/toluene linear gradient 5/95 to 11/89	C ₂₁ H ₁₈ N ₄ O. 0.05 H ₂ O Calc: C, 73.47; H, 5.31; N, 16.32. Found: C, 73.07; H, 5.40; N, 16.01.
					
					
361	Ex. 180		 HCl	Ethanol/methylene chloride/aq. NH ₃ 10/90/1	C ₂₁ H ₁₈ N ₄ O. HCl Calc: C, 66.58; H, 5.06; N, 14.79; Cl, 9.36. Found: C, 66.39; H, 5.04; N, 14.73; Cl, 9.32.
			 HCl + 0.25 H ₂ O		

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Example 362 A and B+ 0.25 H₂O+ 0.25 H₂O

To a stirred solution of 764 mg of the tosylate prepared according to example 186 in 10 ml of DMF was placed 1 g of K₂CO₃ and 326 mg of 5-nitrobenzimidazole. The reaction mixture was heated to 65° C and was stirred at 65°C under nitrogen atmosphere for 4 hours. The reaction mixture was cooled to room temperature, poured into water and extracted with ethyl acetate. The organic extract was washed with water, dried over Na₂SO₄ and concentrated *in vacuo* to afford a residue which was taken up in 8 ml of 1:1 mixture of ethanol and HCl. The mixture was treated with 800 mg of SnCl₂·2H₂O in 1 ml of concentrated HCl. The mixture was heated on the steam bath for 45 minutes, cooled to room temperature and neutralized 10% NaOH solution. The basic solution was extracted with ethyl acetate. The organic extract was washed with water, dried over Na₂SO₄, concentrated *in vacuo* to yield an oily residue which was chromatographed on silica gel using 92.5% CHCl₃, 7% ethanol, and 0.5% NH₄OH as eluant to provide the title compounds.

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A: Calcd for $C_{22}H_{21}N_3O_1 \cdot 1/4H_2O$:

Calc: C, 75.91; H, 6.23; N, 12.08

Found: C, 75.96; H, 6.10; N, 12.03

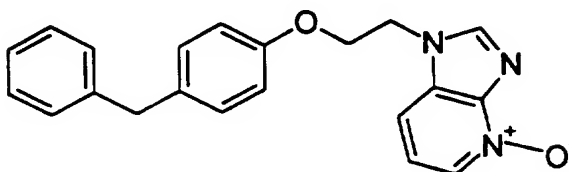
5 B: Calcd for $C_{22}H_{21}N_3O \cdot 1/4H_2O$:

Calc: C, 75.95; H, 6.23; N, 12.08

Found: C, 75.73; H, 6.05; N, 11.94

Example 363

10



15

+ 0.25 H₂O

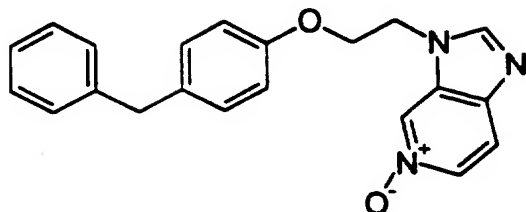
To a stirred solution of 200 mg of the compound prepared in example 338B in 5 ml of CHCl₃, was added 200
20 mg of 80-85% m-chloroperoxybenzoic acid and the mixture was stirred at room temperature for 1 hr. The mixture was diluted with 10 ml of CHCl₃, and was washed with 10% K₂CO₃ solution and water, dried over Na₂SO₄ and concentrated. The residue was chromatographed over
25 silica gel using 85% CHCl₃, 14% ethanol and 1% aqueous NaOH as eluant to yield the title compound as white solid (example 49).

Calcd for $C_{21}H_{19}N_3O_2 \cdot 1/4H_2O$:

Calc: C, 72.09; H, 5.62; N, 12.01

30 Found: C, 71.71; H, 5.50; N, 11.81

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Example 364+ 0.25 H₂O

10

Following the procedure described in example 363 and replacing the compound of example 338B with the compound of example 340C provided the title compound as white solid.

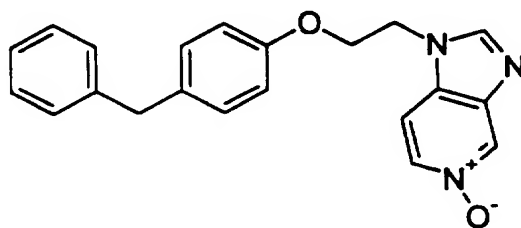
15 Calcd for C₂₁H₁₉N₃O₂·1/4H₂O:

Calc: C, 72.09; H, 5.02; N, 12.01

Found: C, 72.16; H, 5.62; N, 11.96

Example 365

20

+ 0.25 H₂O

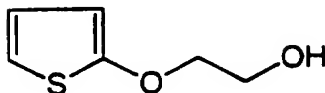
30 Following the procedure described in example 363 and replacing the compound of example 338B with the compound of example 340B provided the title compound as white solid.

Calcd for C₂₁H₁₉N₃O₂·1/4H₂O:

Calc: C, 72.09; H, 5.62; N, 12.01

35 Found: C, 72.31; H, 5.82; N, 12.05

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Example 366

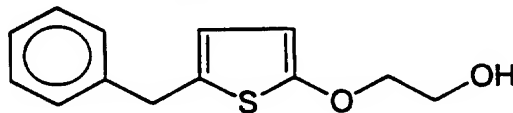
5

To stirred ethylene glycol (200 mL) was added sodium pellets (5.75 g, 250 mmol, Aldrich). After the sodium was dissolved the solution was cooled to room temperature. To this solution was added copper (II) oxide (4.8 g, 60 mmol), and 2-iodothiophene (25 g, 119 mmol). This mixture was then heated at 120°C for 40 hours. The mixture was cooled to room temperature and poured into water (1000 mL). The aqueous mixture was then extracted with two 250 mL portions of ether. The combined ether extracts were washed 3 times with water (2 x 100 mL), saturated brine (100 mL) and dried over MgSO₄. After filtration, the volatile components were removed at reduced pressure on a rotary evaporator. The residue was chromatographed on silica gel gradient eluting with ethyl acetate:hexane (100% hexane to 1:5). This produced 15.9 g (30.3%) of the title compound as an oil.

HRMS (M⁺) for C₆H₈O₂S
Calculated: 144.0245
Found: 144.0245

Example 367

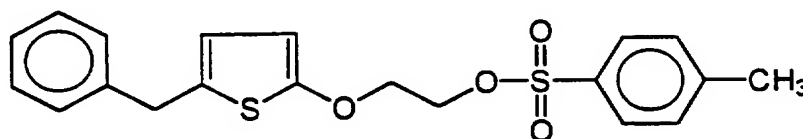
30



To a stirred solution of the product of Example 366 (1 g, 7 mmol) in tetrahydrofuran (20 mL) at -50°C was added n-butyllithium (1.6 M in THF, 10 mL, 16 mmol) dropwise over one minute. The mixture was slowly

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warmed over one hour to -20°C and then cooled to -50°C . The mixture was then treated with benzyl bromide (0.9 mL, 7.6 mmol) and warmed to room temperature over one hour. The mixture was poured into water (50 mL), saturated brine (25 mL) and dried over MgSO_4 . After filtration, the volatile components were removed at reduced pressure on a rotary evaporator. The crude product was used in Example 368 without further purification.

Example 368

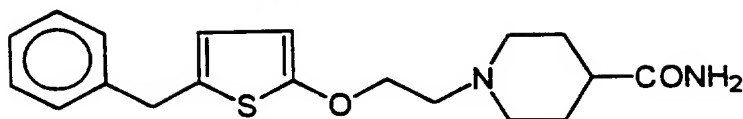
To a cooled (0°C) and stirred solution of the product of Example 367 (1.6 g, 7 mmol) in methylene chloride (25 mL) was added pyridine (2.2 mL, 28 mmol) and p-toluenesulfonyl chloride (2.7 g, 14 mmol). The mixture was allowed to warm to room temperature and stirred for 18 hours. The mixture was poured into water (100 mL) and extracted with two 50 mL portions of ethyl acetate. The combined ethyl acetate extracts were washed 2 times with water (2 x 25 mL), saturated brine (25 mL) and dried over MgSO_4 . After filtration, the volatile components were removed at reduced pressure on a rotary evaporator. The residue was chromatographed on a reverse phase column gradient eluting with methanol-water. This produced 0.64 g (24%) of the title compound.

HRMS (M^+) for $\text{C}_{20}\text{H}_{20}\text{S}_2\text{O}_4$

Calculated: 388.0803

Found: 388.0803

- 214 -

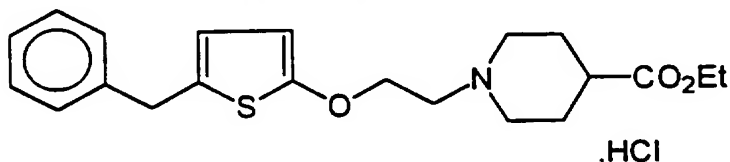
Example 369

5

To a stirred solution of the product of Example 368 (0.1 g, 0.26 mmol) and isonipecotamide (0.06 g, 0.5 mmol, Aldrich) in N,N-dimethylformamide (5 mL) was added anhydrous potassium carbonate (0.25 g) in one portion. This mixture was heated at 80°C for 18 hours. The mixture was poured into water (100 mL) and extracted with 25 mL of ethyl acetate. The ethyl acetate was washed 2 times with water (2 x 25 mL), saturated brine (25 mL) and dried over MgSO₄. After filtration, the volatile components were removed at reduced pressure on a rotary evaporator. The residue was chromatographed on silica gel gradient eluting with hexane:ethyl acetate (1:1 to 100% ethyl acetate) saturated with aqueous concentrated ammonium hydroxide. The solid produced was triturated with ether. This produced 0.02 g (22.3%) of the title compound.

HRMS (M+) for C₁₉H₂₄N₂SO₂: Calculated: 344.1558
Found: 344.1566.

25

Example 370

30

The product from Example 368 (0.1 g, 0.26 mmol) and ethyl isonipecotate (0.08 g, 0.5 mmol, Aldrich) was subjected to the reaction conditions described for the preparation of Example 369. The crude product was chromatographed on silica gel eluting with ethyl

35

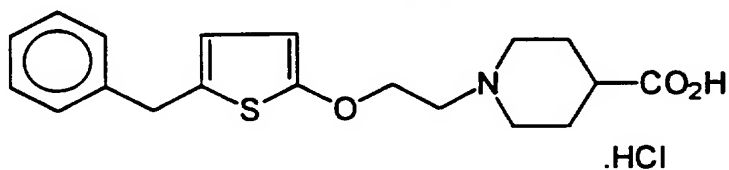
- 215 -

acetate:hexane (1:1) saturated with aqueous concentrated ammonium hydroxide. The product was taken up in ether (5 mL) and treated with hydrogen chloride and the resulting solid was triturated with ether.

5 This produced 0.06 g (56%) of the title compound.

HRMS (M+) for $C_{21}H_{27}NO_3S$:	Calculated:	373.1712
	Found:	373.1715

10

Example 371

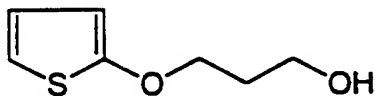
15

To a stirred solution of the product of Example 370 (0.04 g, 0.1 mmol) in tetrahydrofuran (2 mL) was added 6N HCl (5 drops). This solution was heated at 60°C for 5 hours. The volatile components were removed at reduced pressure on a rotary evaporator and the residue was triturated with ether to give the title compound.

20

HRMS (MH+) for $C_{19}H_{23}NO_3S$:	Calculated:	346.1477
	Found:	346.1479.

25

Example 372

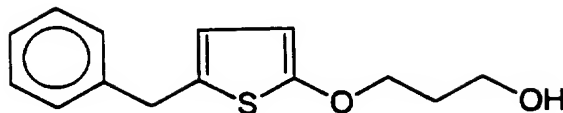
30

1,3-Propanediol (200 mL, Aldrich) was subjected to the reaction conditions described for the preparation of Example 366. This produced 13.2 g (70%) of the title compound.

35

HRMS (M+) for $C_7H_{10}O_2S$:	Calculated:	158.0402
	Found:	158.0397.

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Example 373

5

The product from Example 372 (6 g, 37.9 mmol) was subjected to the reaction conditions described for the preparation of Example 362. The residue was chromatographed on a reverse phase column gradient eluting with methanol-water. This produced 0.76 g (7.9%) of the title compound.

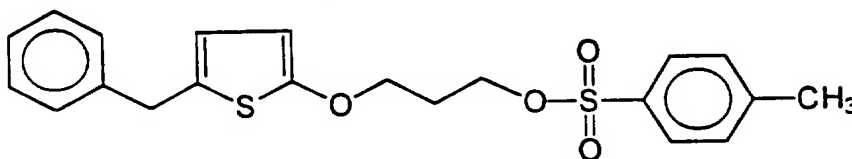
10

HRMS (M+) for $C_{14}H_{16}O_2S$:

Calculated: 248.0871

Found: 248.0874.

15

Example 374

20

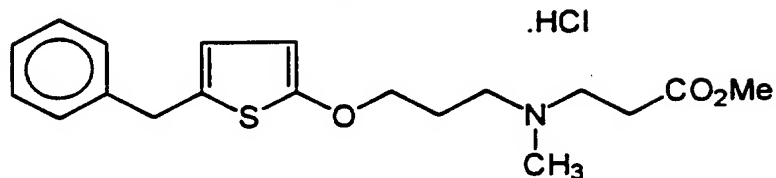
The product from Example 373 (0.5 g, 2.01 mmol) was subjected to the reaction conditions described for the preparation of Example 368. The crude product was chromatographed on silica gel gradient eluting with ethyl acetate:hexane (1:19 to 1:9). This produced 0.53 g (65%) of the title compound.

25

NMR ($CDCl_3$): 7.76 (d, 2H), 7.35-7.19 (complex, 7H), 6.37 (d, 1H), 5.90 (d, 1H), 4.16 (T, 2H), 3.98 (S, 2H), 3.95 (T, 2H), 2.39 (S, 3H), 2.06 (Pent., 2H).

30

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Example 375

10 The product from Example 374 (0.2 g, 0.5 mmol) and N-methyl- β -alanine was subjected to the reaction conditions described for the preparation of Example 369. The crude product was chromatographed on silica gel eluting with ethyl acetate:hexane (1:4). The product was taken up in ether (5 mL) and treated with hydrogen chloride and the resulting solid was

15 triturated with ether. This produced 0.08 g (42%) of the title compound.

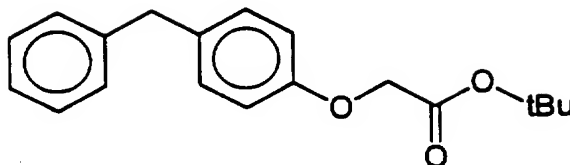
HRMS (MH⁺) for C₁₉H₂₅SNO₃: Calculated: 348.1633
Found: 348.1651.

20

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Example 376

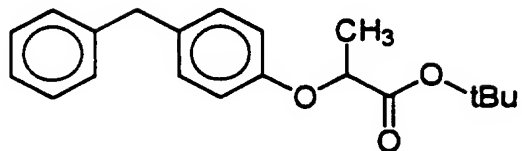
5



To a stirred suspension of sodium hydride (prewashed with hexane) (3.2g, 50% oil dispersion) in DMF (100 ml) 4-hydroxydiphenylmethane (10g, 54 mmol) was added. The reaction mixture stirred at room temperature for 30 minutes, cooled to 0°C and tetra-n-butylammonium iodide (cat) followed by tert butylbromo acetate (9.6 ml, 1.1 eq) were added. After 30 minutes the reaction mixture was quenched into a mixture of 2N hydrochloric acid/ice and the resulting solution extracted into diethyl ether. The organic extracts were separated, washed with saturated potassium hydrogen sulfate, followed by saturated potassium carbonate, dried (Na₂SO₄) and evaporated to afford the title compound as a yellow oil.

The resulting yellow oil was further purified by chromatography on silica (eluant: diethyl ether/hexane 10/90) to afford the title compound as a colorless oil (15.02 g). NMR spectrum of this oil was consistent with the proposed structure.

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Example 377

5

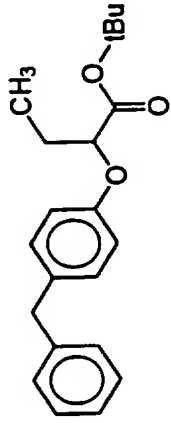
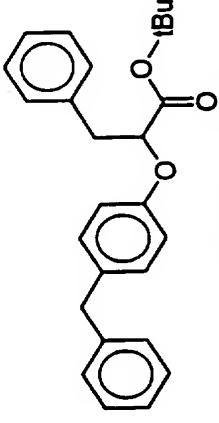
To a stirred solution of the t-butyl ester from example 376 (2.78g, 10mmol) in THF (100ml) at -78°C, lithium diisopropylamide (6ml, 2M solution (Aldrich), 1.2 eq) was added. The reaction mixture was stirred at -78°C for 40 min, quenched with methyl iodide (1ml, excess) and allowed to attain room temperature. The reaction mixture was evaporated, and partitioned between diethyl ether and saturated potassium hydrogen sulfate solution. The organic extracts were separated, dried (Na₂SO₄) and evaporated to afford a yellow oil (3.2g). The crude product was purified by chromatography on silica (eluant; hexane/diethyl ether, 80/20) to afford the title compound (2.76g,).

20

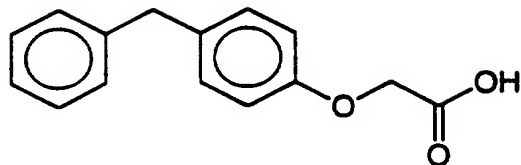
This compound was characterized by NMR and fully authenticated at the next step (Example 381).

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TABLE 20

Ex. No.	Compound	Alkylating Agent	Analysis
378		EtI	$C_{21}H_{26}O_3$; Calc: C, 77.27; H, 8.03. Found: C, 76.95; H, 8.32.
379		BnBr	$C_{26}H_{28}O_3$; Calc: C, 79.46; H, 7.31. Found: C, 79.31; H, 7.32.

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Example 380

5

To a stirred solution of t-butyl ester from
example 376 (9.60 g, 34.5 mmol) in methylene chloride
10 (50 ml) and methanol (5 ml) at 0°C trifluoroacetic acid
(50 ml, prechilled in ice) was added. The reaction
mixture was stirred at 0°C for 20 minutes, then allowed
to attain room temperature overnight. The reaction
mixture was evaporated to afford an off white solid
15 which was recrystallized from diethyl ether/hexane to
yield the title compound (6.12 g).

Analysis Calculated for $C_{15}H_{14}O_3 \cdot 0.1 H_2O$:

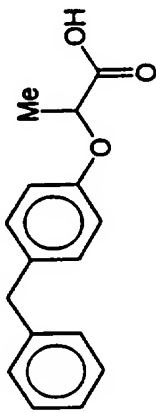
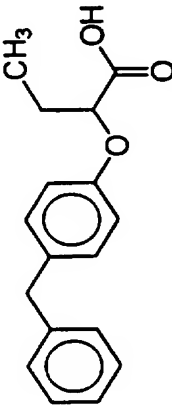
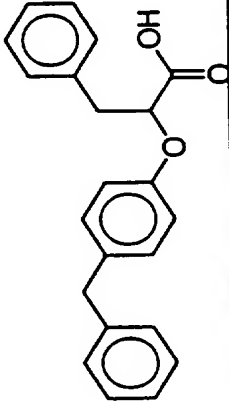
Calculated: C, 73.82; H, 5.86.

20 Found: C, 73.77; H, 5.76.

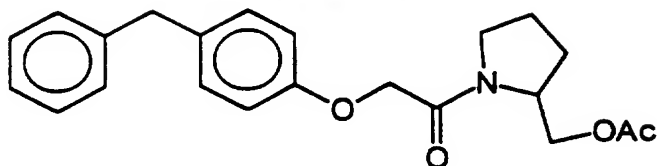
Following examples were carried out (i.e. examples
381, 382, 383) as described in Example 380.

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TABLE 21

Ex. No.	Compound	Starting Ester	Analysis
381		Ex. 377	$C_{16}H_{18}O_3$: Calc: C, 73.69; H, 6.38. Found: C, 73.63; H, 6.24.
382		Ex. 378	$C_{17}H_{18}O_5$: Calc: C, 74.30; H, 6.78. Found: C, 74.21; H, 6.69.
383		Ex. 379	$C_{22}H_{20}O_5$, 0.6 H_2O : Calc: C, 76.99; H, 6.23. Found: C, 76.90; H, 5.88.

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Example 384

5

To a stirred solution of the acid from example 380 (800 mg, 3.31 mmol) in dimethylformamide (10 ml) and pyridine (2 ml), disuccinyl carbonate (842 mg) and 4-dimethylaminopyridine (cat) were added. The reaction mixture was stirred at room temperature for 50 minutes and then D-prolinol (500 mg) was added. The reaction mixture was stirred overnight, evaporated, and partitioned between ethyl acetate and saturated potassium hydrogen sulfate solution. The organic extracts were separated, dried (Na_2SO_4) and evaporated to afford an off white solid (crude yield = 1.20 g). The crude solid was dissolved in acetic anhydride, to which pyridine (2-drops) were added. The reaction mixture was stirred for 4 hours, quenched with saturated sodium hydrogen carbonate solution and extracted into ethyl acetate. The organic extracts were separated, dried (Na_2SO_4) and evaporated to afford an off white solid. This crude product was further purified by chromatography on silica (eluant; diethyl ether) to afford the title compound (920 mg).

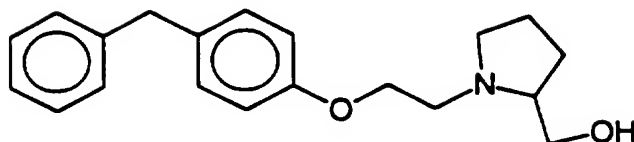
Analysis calculated for $\text{C}_{22}\text{H}_{23}\text{NO}_4 \cdot 0.15 \text{ H}_2\text{O}$:

30 Calc: C, 71.39; H, 6.89; N, 3.78.
Found: C, 71.37; H, 6.82; N, 3.70.

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Example 385

5



10 The title compound was prepared from the amide described in example 384 (650 mg) in a manner identical to that described in example 397. This afforded the title compound (360 mg).

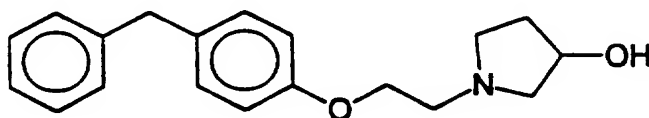
Analysis calculated for $C_{20}H_{23}NO_2 \cdot 0.1 HCl \cdot 0.8 H_2O$:

Calc: C, 66.30; H, 7.68; N, 3.87.

15 Found: C, 66.13; H, 7.71; N, 4.21.

Example 386

20



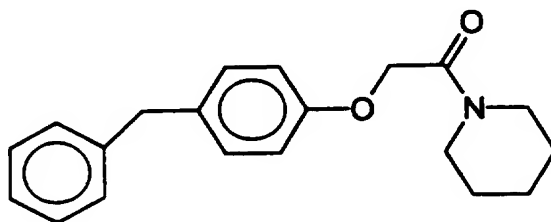
25 The title compound was prepared as described in examples 384 and 385 above, replacing D-prolinol with 3-hydroxy pyrrolidine, to afford the title compound (100 mg).

Analysis calculated for $C_{19}H_{23}NO_2 \cdot 0.1 HCl \cdot 0.5 H_2O$:

30 Calc: C, 66.56; H, 7.35; N, 4.09.

Found: C, 66.42; H, 7.06; N, 4.53.

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Example 3871-(1-piperidinyl)-2-[4-(phenylmethyl)-
phenoxy]ethanone

245 mg of sodium hydride (50% in oil) washed with hexane to remove the oil, was added to the solution of 920 mg of 4-hydroxydiphenylmethane in 10 ml of N,N-dimethylformamide. The mixture was stirred at room temperature under nitrogen atmosphere for 10 minutes, and then 806 mg of 1-(chloroacetyl)piperidine was added to the mixture. The reaction mixture was poured into water and was extracted with ether. The ether extract was washed with water, followed by 10% NaOH solution, dried over Na₂SO₄. The solvent was removed by evaporation under reduced pressure to provide crude product which was crystallized from ether/hexane to provide 656 mg of the title compound as white crystalline solid.

Analysis calculated for C₂₀H₂₃NO₂:

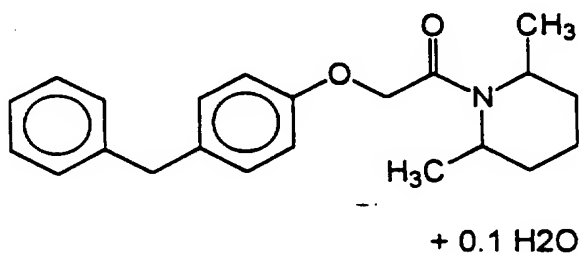
Calc: C, 77.64; H, 7.49; N, 4.53.

Found: C, 77.83; H, 7.49; N, 4.49.

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Example 388

1-(2,6-dimethylpiperidin-1-yl)-2-[4-(phenylmethyl)-
phenoxy]ethanone

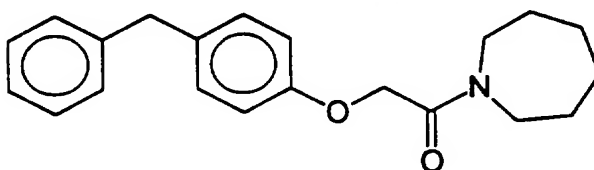


Following the procedure described in example 387 and replacing 1-(chloroacetyl)piperidine with 1-(chloroacetyl)-2,6-dimethylpiperidine yielded the title compound.

Analysis calculated for C₂₂H₂₇N₂O·0.1H₂O:

Calc: C, 77.89; H, 8.08, N, 4.13.

Found: C, 77.84, H, 8.16; N, 4.13.

Example 389

To stirred solution of the acid from example 380 (800 mg, 3.31 mmol) in dimethylformamide (10 ml) and pyridine (2 ml), disuccinyl carbonate (842 mg) and 4-dimethylaminopyridine (cat) were added. The reaction mixture was stirred at room temperature for 50 minutes and then hexamethyleneimine (330 mg) was added. The reaction mixture was stirred overnight, evaporated, and partitioned between ethyl acetate and saturated

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potassium hydrogen sulfate solution. The organic
extracts were separated, dried (Na_2SO_4) and evaporated
to afford an off white solid (crude yield = 1.1 g). The
crude product was purified by chromatography on silica
5 (eluant; diethyl ether/hexane, 70/30) to afford the
title compound (800 mg).

Analysis calculated for $\text{C}_{11}\text{H}_{12}\text{NO}_2 \cdot 0.15 \text{ H}_2\text{O}$:

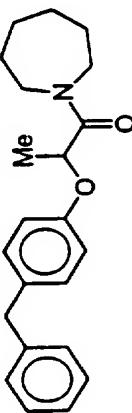
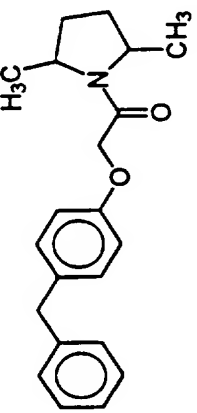
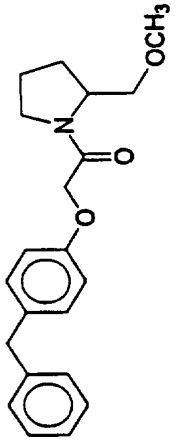
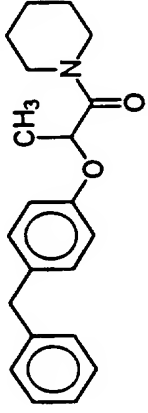
Calc: C, 77.34; H, 7.82; N, 4.29.

10 Found: C, 77.40; H, 7.84; N, 4.30.

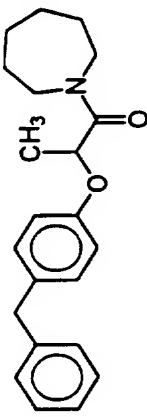
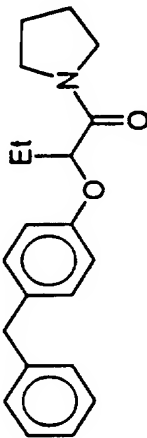
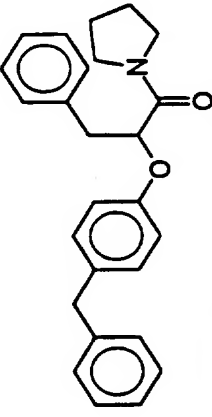
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The compounds described in the following table were prepared essentially as described in Example 384.

TABLE 22

Ex. No.	Compound	Starting Amine and Acid	Analysis
390		Azacycloheptane and Ex. 381	$C_{22}H_{27}NO_2$ Calc: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.15; H, 7.85; N, 4.12.
391		2,5 Dimethyl pyrrolidine and Ex. 380	$C_{21}H_{26}NO_2 \cdot 0.1H_2O$ Calc: C, 77.50; H, 7.81; N, 4.31. Found: C, 77.48; H, 7.83; N, 4.36.
392		S-(+)-2-(methoxymethyl)-pyrrolidine and Ex. 380	NMR spectrum was consistent with the proposed structure. Compound was fully characterized in the next step. See Example No. 400.
393		piperidine and Ex. 381	$C_{21}H_{26}NO_2 \cdot 0.1H_2O$ Calc: C, 77.55; H, 7.81; N, 4.31. Found: C, 77.56; H, 7.79; N, 4.36.

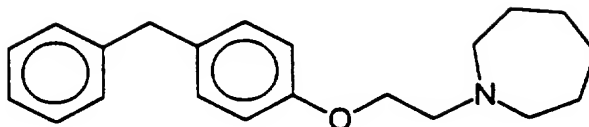
- 229 -

Ex. No.	Compound	Starting Amine and Acid	Analysis
394		hexahydroazepine and Ex. 381	Compound was fully characterized in the next step. See Example No. 397.
395		pyrrolidine and Ex. 382	$C_{20}H_{23}NO_2$, 0.6 H_2O : Calc: C, 75.46; H, 7.90; N, 4.19. Found: C, 75.44; H, 8.14; N, 4.03.
396		pyrrolidine and Ex. 383	$C_{26}H_{27}NO_2$, 1.3 H_2O : Calc: C, 75.70; H, 7.33; N, 3.40. Found: C, 75.64; H, 7.02; N, 3.24.

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Example 397

5



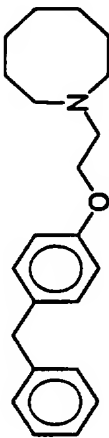
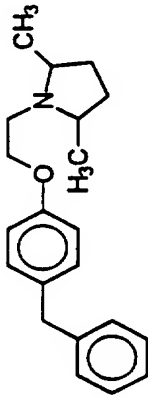
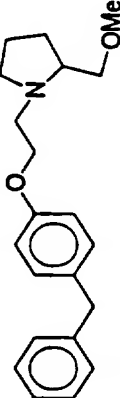
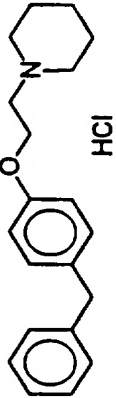
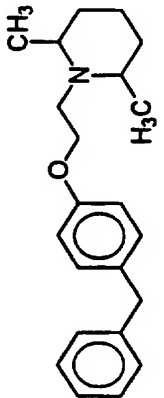
To a stirred suspension of Lithium aluminum
hydride (400 mg, excess) in THF (10 ml) at room
temperature, the amide for example 389 (700 mg) was
10 added. The reaction mixture was stirred at room
temperature for 3 hours, quenched with water (1 ml) and
then diluted with ethyl acetate (50 ml). The reaction
mixture was filtered and the mother liquors evaporated
to afford a colorless oil. The free amine was
15 converted to its HCl salt and crystallized from
ethanol/diethyl ether to afford the title compound
(545 mg).

Analysis calculated for $C_{21}H_{27}NO \cdot 1 HCl \cdot 0.2 H_2O$:

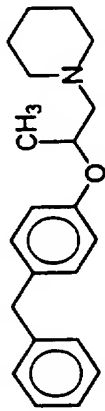
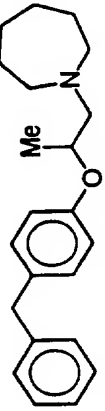
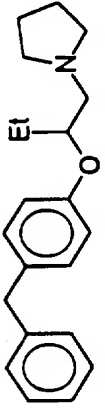
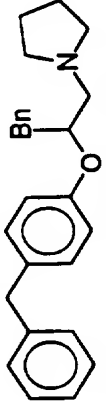
20 Calc: C, 72.17; H, 8.19; N, 4.01.
Found: C, 72.21; H, 8.21; N, 4.07.

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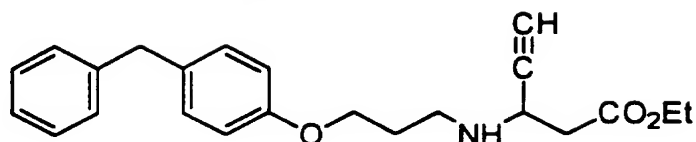
TABLE 23

Ex. No.	Compound	Starting Material	Analysis
398		Ex. 390	$C_{21}H_{29}NO \cdot 1 HCl$ Calc: C, 73.41; H, 8.40; N, 3.89. Found: C, 73.04; H, 8.58; N, 3.99.
399	 HCl	Ex. 391	Calcd for $C_{21}H_{27}NO \cdot HCl$: Calc: C, 72.92; H, 8.10; N, 4.05. Found: C, 72.70; H, 8.47; N, 3.99.
400		Ex. 392	$C_{21}H_{27}NO_2 \cdot HCl \cdot 1/2 H_2O$: Calc: C, 68.00; H, 7.88; N, 3.78. Found: C, 67.91; H, 7.75; N, 4.06.
401	 HCl	Ex. 387	$C_{20}H_{28}NO \cdot HCl$: Calc: C, 72.38; H, 7.90; N, 4.22. Found: C, 72.23; H, 7.93; N, 4.21.
402	 HCl	Ex. 388	$C_{22}H_{28}NO \cdot HCl$: Calc: C, 73.41; H, 8.40; N, 3.89. Found: C, 73.43; H, 8.49; N, 3.59.

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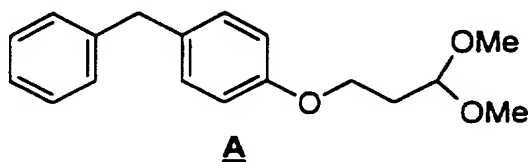
Ex. No.	Compound	Starting Material	Analysis
403		Ex. 393	$C_{20}H_{26}NO \cdot 1 HCl \cdot 0.2 H_2O$: Calc: C, 72.17; H, 8.19; N, 4.01. Found: C, 72.26; H, 8.12; N, 4.10.
404		Ex. 394	$C_{22}H_{28}NO \cdot 1 HCl \cdot 0.15 H_2O$: Calc: C, 72.87; H, 8.42; N, 3.86. Found: C, 72.85; H, 8.49; N, 4.00.
405		Ex. 395	$C_{21}H_{27}NO \cdot 1 HCl \cdot 0.2 H_2O$: Calc: C, 72.17; H, 8.19; N, 4.01. Found: C, 72.21; H, 8.19; N, 3.96.
406		Ex. 396	$C_{28}H_{36}NO \cdot 1 HCl \cdot 0.1 H_2O$: Calc: C, 76.21; H, 7.43; N, 3.42. Found: C, 76.10; H, 7.45; N, 3.31.

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Example 407

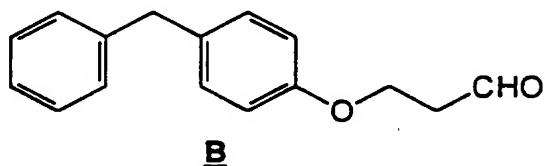
1) 3-Bromo propionaldehyde dimethyl acetal was reacted with 4-hydroxy diphenyl methane as in example 216 and was purified through column chromatography to afford intermediate A.

10



2) 1 g of intermediate A in 10 ml of THF was added 0.5 ml of H₂O. P-toluenesulfonic acid 50 mg was added and heated to 70° overnight. The solvent was removed and the organic material was extracted with 30 ml ether. The ethereal extracts were dried (Na₂SO₄) and evaporated to afford to intermediate aldehyde B.

20



3) The intermediate B 240 mg in 3 ml of EtOH was added 177 mg of ethyl 3-amino pentyn-1-carboxylate (The NutraSweet Company) and 1 mmole of KOH (56 mg) and was stirred for 1/2 hr. 63 mg of NaBH₃CN was then added and the reaction was worked up as example 12 and after chromatography to provide 20 mg of the title compound as a colorless oil.

30

35

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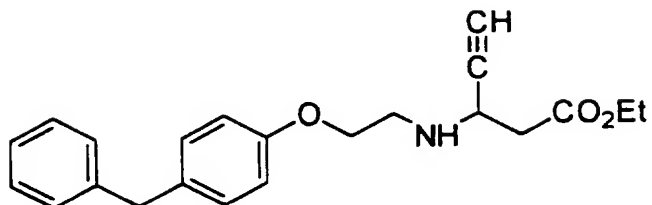
Analysis for $C_{23}H_{27}NO_3 \cdot 0.1H_2O$

		<u>Theory</u>	<u>Found</u>
5	C	74.18	74.17
	H	7.36	7.66
	N	3.75	3.77

Example 408

10

15



The title compound was prepared in accordance with example 407 except that bromoacetaldehyde diethyl acetal was used instead of 3-bromopropionaldehyde dimethyl acetal.

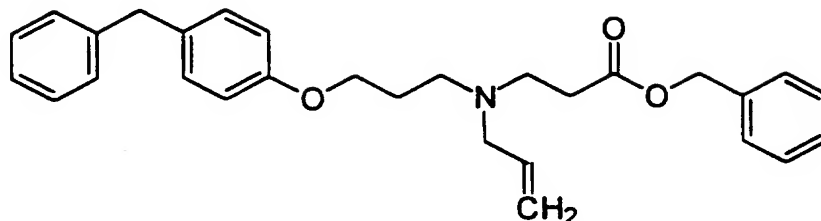
Analysis for $C_{22}H_{25}NO_3$

		<u>Theory</u>	<u>Found</u>
25	C	75.19	69.79
	H	7.17	7.11
	N	3.98	4.21

- 235 -

Example 409

5



10

To a stirred solution 100 mg of the compound of example 261 in 5 ml DMF was added NaH 12 mg (60% dispersion, Aldrich). After 10 minutes of stirring, 30 mg benzyl bromide (Aldrich) in 2 ml DMF was added dropwise stirred at room temperature for 1 hr. Organic material was extracted with 30 ml ether and was washed with H₂O(5 ml x 3), dried, and purified by column chromatography to provide 60 mg of the title compound as a colorless oil.

15

20

Analysis for C₂₉H₃₃NO₃

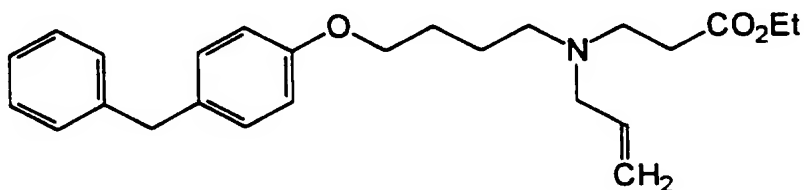
	<u>Theory</u>	<u>Found</u>
25 C	78.52	78.18
H	7.50	7.50
N	3.16	3.06

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Example 410Preparation of ethyl [[4-[4-(phenylmethyl)phenoxy]-
butyl](2-propenyl)amino]propanoate

5

10



150 mg of the compound of example 271 was reacted in accordance with the method of example 409 to provide 100 mg of the title compound as a colorless oil.

15

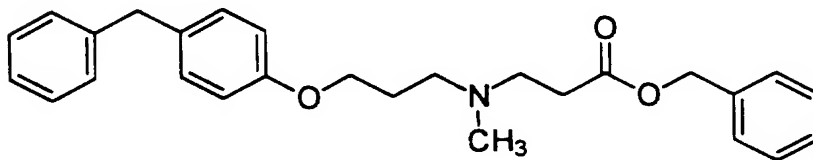
Analysis for $C_{25}H_{33}NO_3$

		<u>Theory</u>	<u>Found</u>
20	C	75.92	75.94
	H	8.41	8.59
	N	3.54	3.43

Example 411

25

30



To 100 mg of the compound of example 261 and 0.1 ml of 37% aq HCHO in 2 ml of CH_3CN was added 25 mg of $NaBH_3CN$ and the reaction mixture stirred for 15 min.

35 Two drops of glacial acetic acid was added and the reaction mixture was stirred for another 30 min. Solvent was removed in vacuo and the remaining mixture

- 237 -

was basicified with 15%KOH to pH 8 and the organic material was extracted with 20 ml ether. The organic phase was washed with H₂O (10 ml x 3) and was dried. It was filtered and the resulting oily substance was purified by silica gel chromatography using 50:50:1-EtOAc:tol:TEA as eluant to provide 90 mg of the title compound.

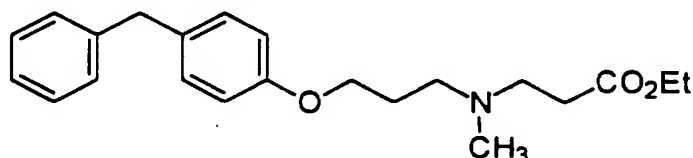
Analysis for C₂₅H₂₇NO₃·0.2H₂O

10

	<u>Theory</u>	<u>Found</u>
C	76.39	76.10
H	7.03	7.05
15 N	3.56	3.48

Example 412

20



170 mg of the compound of example 265 was converted to 100 mg of the title compound using the procedure described in example 411.

25

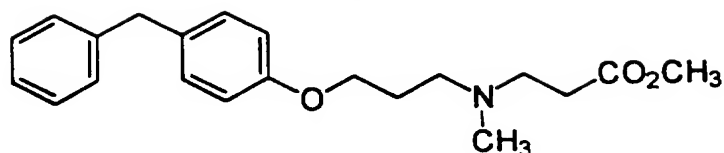
Analysis for C₂₂H₂₉NO₃

30

	<u>Theory</u>	<u>Found</u>
C	74.33	74.28
H	8.22	8.44
N	3.94	4.00

35

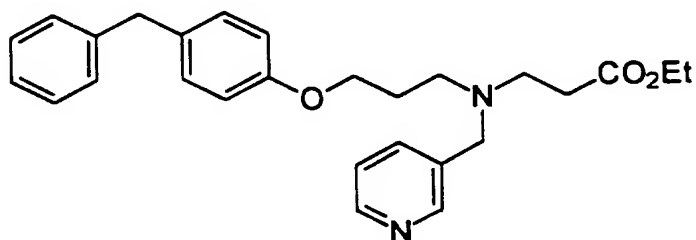
- 238 -

Example 413H₂O

160 mg of the compound of example 267 was converted to 37.4 mg of the title compound following the procedure of example 411.

Analysis for C₂₁H₂₇NO₃·H₂O

	<u>Theory</u>	<u>Found</u>
C	70.17	69.85
H	8.13	8.04
N	3.90	3.92

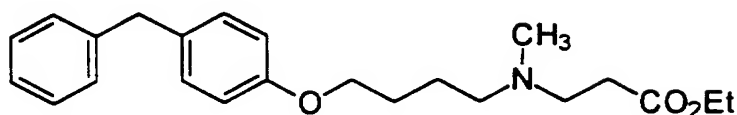
Example 414+ 0.2 H₂O

770 mg of the compound of example 265 was reacted with 3-pyridine carboxaldehyde (Aldrich) 0.12 g following the procedure of example 411. Silica gel chromatography afforded 0.7 g of the title compound.

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Analysis for $C_{27}H_{32}N_2O_3 \cdot 0.2H_2O$

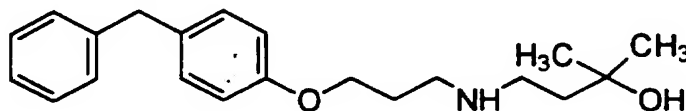
		<u>Theory</u>	<u>Found</u>
5	C	74.70	74.31
	H	7.06	7.49
	N	6.45	6.28

Example 415+ 0.4 Et₃N 0.2 H₂O

640 mg of the compound of example 272 was reacted in accordance with the method described in example 411 to obtain 350 mg of the title compound as a colorless oil.

Analysis for $C_{23}H_{31}NO_3 \cdot 0.4 Et_3N \cdot 0.2H_2O$

		<u>Theory</u>	<u>Found</u>
25	C	73.76	73.43
	H	9.11	8.66
	N	4.74	4.33

Example 416+ 0.5 H₂O

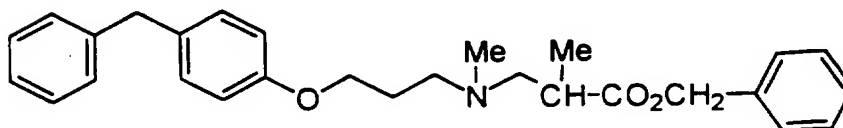
- 240 -

The compound of example 265 (267 mg) in anhyd. THF was cooled to 0°C and 2 mmol of MeMgCl in THF was added during 1/2 hr and stirred at room temperature for 1/2 hr. 2 ml of aqueous NH₄Cl solution was added dropwise at 0°C and the solvent was removed in vacuo. The organic material was extracted with 30 ml ether and was chromatographed in a silica gel column using 20:80:1-EtOH:EtOAc-TEA as eluant to provide 75 mg of the title compound as a colorless oil.

Analysis for C₂₁H₂₉NO₂·0.5H₂O

		<u>Theory</u>	<u>Found</u>
15	C	74.96	74.80
	H	8.99	8.35
	N	4.16	4.65

Example 417



20

1.13 g of the compound of example 411 in THF was added dropwise to 3 mmol of LDA in 20 ml of THF at -78° during 1/2 hr. After 1/2 hr at -78°, 5 mmol of methyl iodide was added and reaction mixture was warmed to room temperature. Solvent was removed in vacuo and organic material was extracted with 50 ml ether and was dried. The desired product, 590 mg of the title compound, was obtained from column chromatography as a colorless oil.

35

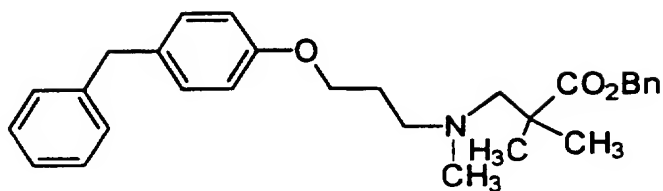
Analysis for C₂₈H₃₃NO₃·0.2H₂O

- 241 -

	<u>Theory</u>	<u>Found</u>
C	77.28	77.00
H	7.74	7.86
5 N	3.22	3.07

Example 418

10



15

Product of example 417, (290 mg) was subjected to conditions described in example 417 and after chromatography on silica gel, a colorless oil was obtained, 21.4 mg.

20

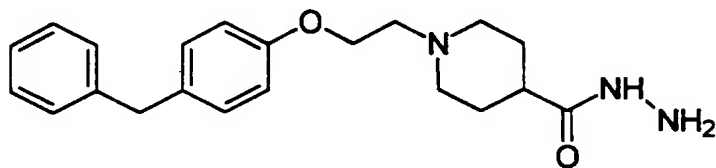
Analysis for $C_{29}H_{35}NO_3$, EtOAc

	<u>Theory</u>	<u>Found</u>
25 C	74.27	74.54
H	8.12	7.76
N	2.62	2.66

30

Example 419

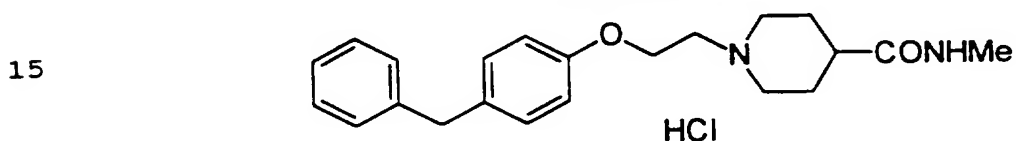
35



- 242 -

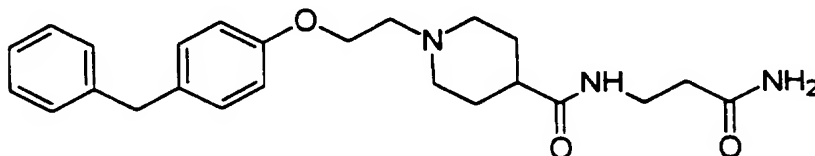
To a stirred solution of 350 mg of the ester of example 245 in 3 ml of n-butanol was added 1 g of hydrazine hydrate and the mixture was heated to reflux and was allowed to reflux under nitrogen atmosphere for 6 hours. The mixture was cooled to room temperature. The solvent was removed by evaporation under reduced pressure to give the crude oily gum, which upon crystallization from diethyl ether provided the title compound as white solid.

Calcd for $C_{21}H_{27}N_3C_2O \cdot 2H_2O$: C, 70.64; H, 7.73; N, 11.77.
Found: C, 70.62; H, 7.88; N, 11.71.

Example 420

Following the procedure described in example 419 and replacing hydrazine hydrate with 40% methyl amine provided the title compound.

Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95.
Found: C, 74.67; H, 8.48; N, 7.88.

Example 421

To a stirred solution of 600 mg of the compound of example 249 in 10 ml of ethanol was condensed 1 ml of liquid ammonia and the mixture was heated in a pressure vessel to 85° C under 200 psi for 4 hours. The mixture was cooled and filtered. The filtrate was concentrated under vacuo to give an oily gum which was chromatographed on silica using 85% $CHCl_3$: 14% ethanol:

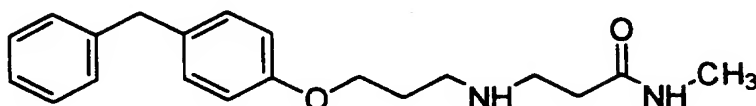
- 243 -

1% NH₄OH as mobile phase to provide 180 mg of the title compound.

Calcd for C₂₄H₃₁N₃O₃: C, 70.39; H, 7.63; N, 10.26

Found: C, 70.17; H, 7.92; N, 10.19

5

Example 422

10

+ 0.3 H₂O

150 mg (0.44 mmol) of the compound of example 265 were dissolved in 10 ml of 40% methylamine (wt.% solution in water). A catalytic amount of NaCN was added and the reaction was stirred at 50° C for 2 hours. The reaction was cooled and the mixture was diluted with 50 ml of H₂O and then extracted with two 25 ml portions of EA. The organic layers were combined, dried and concentrated. Chromatography was carried out on a 1 mm chromatotron plate (90% EA\9% MeOH\1 % triethylamine) to afford 100 mg of pure product.

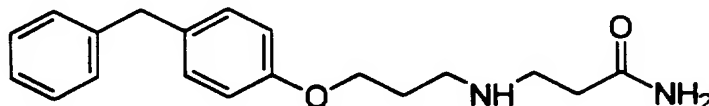
20

Calcd for C₂₀H₂₆N₂O₂ 0.3 H₂O:

Calculated: C, 72.39; H, 8.08; N, 8.44.

25

Found: C, 72.36; H, 8.09; N, 8.22.

Example 423

30

+ 0.3 H₂O

35

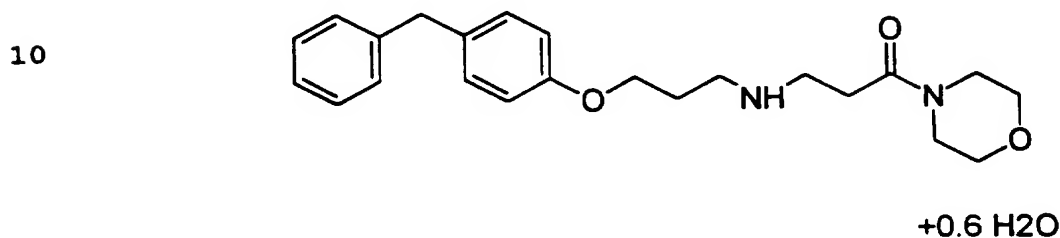
- 244 -

The title compound was prepared essentially as described in Example 422 except that ammonium hydroxide was used instead of methylamine.

Analysis Calcd. for $C_{19}H_{24}N_2O_2 \cdot 0.3 H_2O$

5 Calc: C, 71.81; H, 7.80; N, 8.81.
 Found: C, 72.10; H, 7.94; N, 8.55.

Example 424

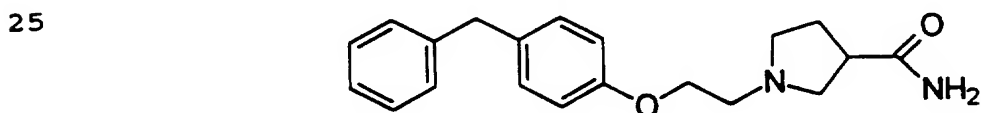


15

The title compound was prepared essentially as described in Example 422 except that morpholine was used instead of methylamine.

20 Calc: C, 70.24; H, 8.00; N, 7.12.
 Found: C, 70.09; H, 8.13; N, 7.46.

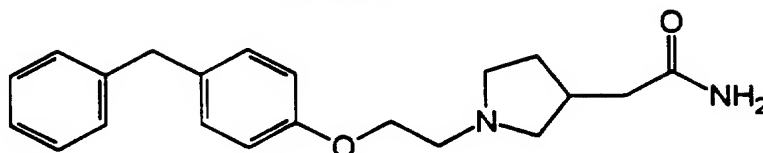
Example 425



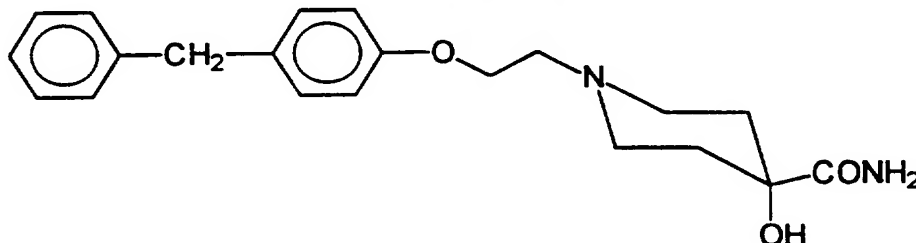
30 The product from Example 276 (0.20 g) was stirred
in concentrated NH_4OH (3 mL) with catalytic NaCN at
reflux in a sealed vial for 23 h. The mixture was
cooled and poured into EtOAc and water. The EtOAc
layer was separated, washed with brine, dried over
Na₂SO₄ and concentrated. Flash chromatography on silica
35 gel using a gradient of 99:1:0.5 to 97:3:0.5
CH₂Cl₂/MeOH/ NH_4OH gave the title compound (0.052 g) as a

- 245 -

colorless oil: Anal. calc'd for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.63. Found: C, 74.12; H, 7.76; N, 8.44.

Example 426

The product from Example 275 (254 mg, 0.72 mmol) and a catalytic amount of sodium cyanide were dissolved in 10 mL ammonium hydroxide. The reaction was refluxed for 12 hours. After cooling to RT, the reaction was neutralized with 10% HCl. The aqueous phases was extracted with 4 X 30 mL ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to afford the crude product as a white solid. The product was chromatographed (silica gel, methanol/methylene chloride/ammonium hydroxide 2/97.5/0.5) to afford the pure product as a white solid. The product had the following properties: mp 106-107°C. Anal. calcd for $C_{22}H_{27}NO_3$: C, 74.53; H, 7.74; N, 8.28. Found C, 74.36; H, 7.66; N, 8.12.

Example 427

A solution of 153 mg of the product from example 305 in 5 mL of ethanol and 5 mL of concentrated ammonium hydroxide solution was prepared and placed in a Parr bottle. The vessel was stoppered and stirred at room temperature for 48 hours. The reaction mixture

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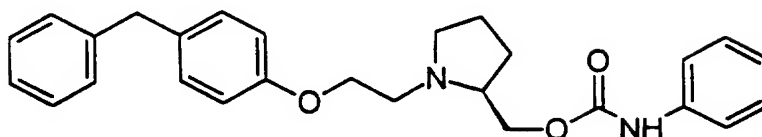
was concentrated and the residue was purified on prep plates eluting with 89.5% CHCl₃-10.0% ethanol-0.5% NH₄OH to yield 59 mg of white powder.

5 Analysis for C₂₁H₂₆N₂O₃ · 1.0 H₂O

Calculated		Found
67.72	C	67.82
7.58	H	7.17
10 7.52	N	7.35

Example 428

15



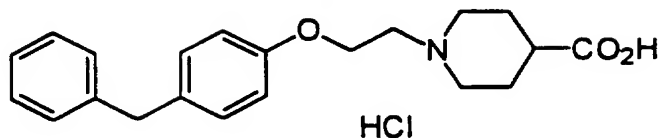
To a stirred solution of the alcohol from example 385 (100 mg, 0.29 mmol) in methylene chloride (5 ml) and triethylamine (0.5 ml, excess) at 0°C, phenyl isocyanate was added. The reaction mixture was stirred overnight, evaporated and partitioned between ethyl acetate and saturated potassium hydrogen sulfate solution. The organic layer was separated, washed with saturated potassium hydrogen carbonate solution followed by brine. The organic extracts were dried (Na₂SO₄) and evaporated to afford a white solid. The crude product was purified by radial chromatography (eluant:ethyl acetate) to afford the title compound (45 mg)

30 Anal. Calc. C₂₇H₃₀N₂O₃:

Calc: C, 75.32; H, 7.02; N, 6.51.

Found: C, 74.96; H, 6.84; N, 6.70.

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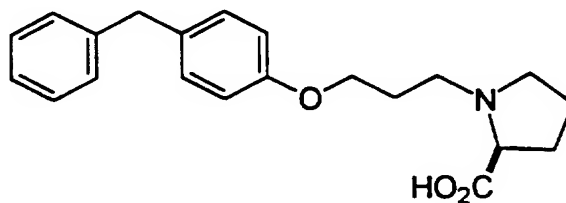
Example 429

To a stirred solution of the ester of example 245 in 8.0 ml of methanol was added 2 ml of 1N NaOH solution. The mixture was heated and allowed to reflux for 1 hour. The reaction mixture was cooled to room temperature and the solvent removed by evaporation under reduced pressure to give a solid residue which was taken up in 10 ml of water and neutralized with 2N HCl until it turned cloudy (pH=4.65). The solution was extracted with ethyl acetate and washed with water and dried over Na₂SO₄. The solvent was removed by evaporation under reduced pressure to give an oily gum which was converted to HCl salt with ethanolic HCl to give 33 mg of the title compound as a white solid.

Calcd for C₂₁H₂₅NO₃·HCl·H₂O:

Calculated: C, 64.03; H, 7.16; N, 3.56

Found: C, 63.53; H, 6.70; N, 3.59

Example 430

The compound of example 228 (0.2 g) was hydrogenated over 4 % Pd/C in 10 ml 3A EtOH, 5 psi for 1.6 hrs. Concentration of the EtOH sol. gave 0.12 g of the title product as white precipitate. The title compound was recrystallized from toluene (m.p. 165-169).

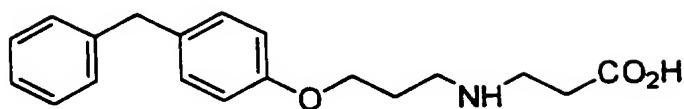
- 248 -

Analysis for $C_{21}H_{24}NO_3 \cdot 0.5H_2O$

	<u>Theory</u>	<u>Found</u>
C	72.60	72.88
5 H	7.25	7.51
N	4.03	3.96

Example 431

10

+ 0.6 H₂O

15

800 mg of the compound of example 261 was hydrogenated over 4% Pd/C in 3A EtOH 20 ml at 5 psi for 2 hr, filtered and recrystallized from 3A EtOH to provide 120 mg of the title compound (m.p. 165-167°).

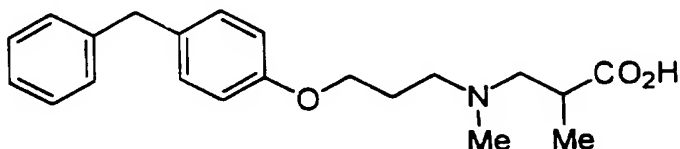
20

Analysis for $C_{19}H_{23}NO_3 \cdot 0.6H_2O$

	<u>Theory</u>	<u>Found</u>
25 C	70.39	70.15
H	7.52	7.29
N	4.32	4.24

Example 432

30



35

0.1 g of the compound of example 417 was hydrogenated over 4% Pd/C in EtOH as described in

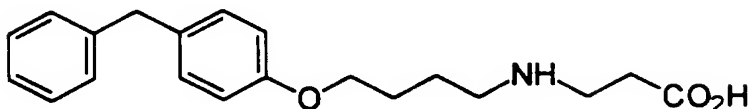
- 249 -

example 431. Removal of the solvent in vacuo followed by silica gel chromatography provided 80 mg of the title compounds as yellow oil.

5 Analysis for $C_{21}H_{27}NO_3$ 0.2 C_7H_8

	<u>Theory</u>	<u>Found</u>
10 C	74.76	74.28
H	8.01	7.95
N	3.89	3.34

15 Example 433



20

The compound of example 273 was hydrogenated as was described for example 431 to afford 70 mg of the title compound, m.p. 140-141.

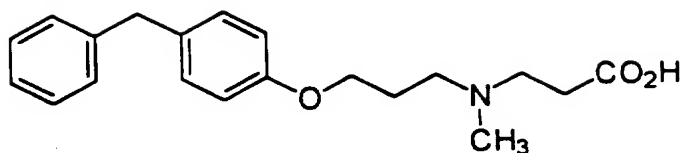
25 Analysis for $C_{20}H_{25}NO_3$

	<u>Theory</u>	<u>Found</u>
30 C	73.37	73.36
H	7.70	7.64
N	4.28	4.20

- 250 -

Example 434

5

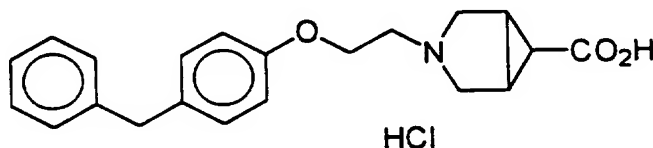


10 The compound of example 411 was hydrogenated as example 431 to afford 30 mg of the title compound as white needles (m.p. 113-116).

Analysis for $C_{20}H_{25}NO_3 \cdot 0.2\text{EtoAc}$

	<u>Theory</u>	<u>Found</u>
15 C	72.40	72.10
H	7.77	8.00
N	4.06	4.41

20

Example 435

25

30 The product from Example 325 (100 mg) was dissolved in 5 ml of freshly distilled THF and was treated with 0.5 mL of 6N HCl and the mixture was refluxed for 4 hours. The reaction mixture was cooled to room temperature and was concentrated in vacuo to yield solid residue, which upon crystallization from ether yielded 78 mg of title compound.

35 Calculated for $C_{21}H_{23}NO_3 \cdot HCl$:

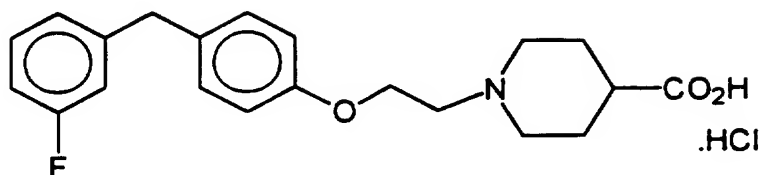
Calc: C, 65.88; H, 6.58; N, 3.66.

Found: C, 66.06; H, 6.83; N, 3.36.

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Example 436

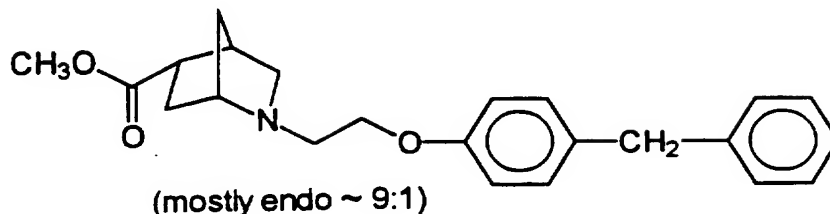
5



10 To a stirred solution of example 309 (30 mg, 0.08 mmols) in THF (2.5 mL) was added 6 N HCl (1 mL) at r.t. The resulting solution was heated to 85°C for 5 hours. The reaction was concentrated in vacuo to give a sticky gum. The residue was washed with Et₂O and then slurried in EtOAc. The solid was collected by vacuum filtration
15 to give 19 mg off-white solid. The resulting product had the following properties: Analysis calcd for C₂₁H₂₅NO₃FCl 0.8 H₂O: C, 61.78; H, 6.57; N, 3.43. Found: C, 61.41; H, 6.09; N, 3.26.
M⁺= 357.

20

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Example 440

10 A solution of 20 mL of 3:1 concentrated hydrochloric acid - water and 725 mg of the product from example 308 was refluxed for 12 hours. The reaction mixture was concentrated and the residue repeatedly azeotroped with toluene and then the residue was dried in vacuo. This material was dissolved in 50 mL of anhydrous methanol

15 and saturated with anhydrous HCl gas with chilling in an ice bath for 1 hour. The reaction mixture was then degassed and concentrated to a small volume and partitioned between 10% K₂CO₃ solution and ethyl acetate. The aqueous portion was extracted with

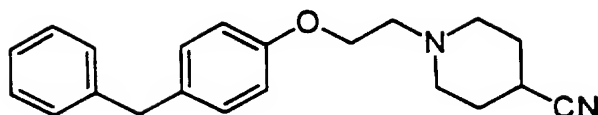
20 additional ethyl acetate and the combined organic extracts washed with saturated NaCl solution, dried over MgSO₄ and concentrated. The product was purified on a silica gel column eluting with 94.5% CH₂Cl₂ - 5.0% CH₃OH - 0.5% NH₄OH to afford 333 mg of viscous oil.

25 Anal. for C₂₃H₂₇NO₃ · 0.25 H₂O:

Calculated			Found
74.67	C		74.60
7.49	H		7.66
3.79	N		3.76

30

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Example 441

HCl

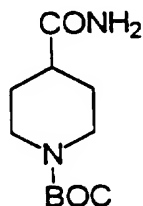
10 To a stirred solution of 300 mg of the amide of
example 242 in 5 ml of THF containing 0.3 ml of
pyridine was added 0.2 ml of trifluoroacetic anhydride
at 0°C and the mixture was stirred at 0° to 5°C for 30
minutes. The reaction was warmed up to room
15 temperature and was allowed to stir at room temperature
for 16 hours. The solvent was removed by evaporation
under reduced pressure to give an oily gum which was
chromatographed on silica gel using 92.5 % CHCl₃: 7%
ethanol and 0.5 % NH₄OH as a mobile phase to give oily
20 gum which was converted into HCl salt followed by
crystallization from ether to provide the title
compound.

Calcd for C₂₁H₂₄N₂O·HCl·0.3 H₂O:

Calculated: C, 69.82; H, 7.12; N, 7.73.

Found: C, 69.36; H, 6.89; N, 7.66.

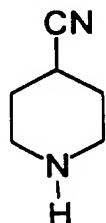
25

Example 442

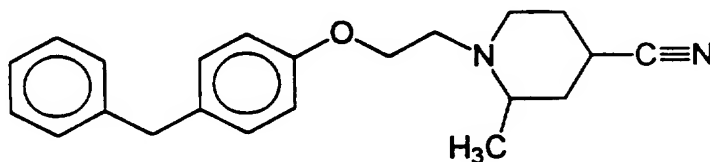
35 To a stirred suspension of isonipecotamide (35 g,
Aldrich) in triethylamine (36 mL) and CHCl₃ (400 mL) at
0°C was added ditertiary butyldicarbonate (55 g,
Aldrich). The mixture was allowed to warm to room

- 255 -

temperature over 3 hr. The volatiles were removed and the residue was taken up in a mixture of CH_2Cl_2 and ether. The organic solution was washed with water, dried over MgSO_4 and concentrated in vacuo to give the title compound, as a white solid (51 g).

Example 443

To a stirred solution of the product of Example 442 (51 g) in pyridine (175 mL) at 0°C was added trifluoroacetic anhydride (38 mL) over 45 min. The mixture was allowed to warm to room temperature over 16 hr. The mixture was concentrated in vacuo to 1/3rd its original volume and poured into ice-cold water. The mixture was extracted with CHCl_3 . The organic phase was washed with water (2 times), dried over MgSO_4 and distilled in vacuo to give the title compound (32 g, Bp = $110^\circ\text{--}115^\circ\text{C}/0.01\text{ mm}$).

Example 444

Following the procedure described in example: 441 and replacing the compound of example 242 with the compound of example 297 yields the title compound as HCl salt. Calcd. for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O} \cdot \text{HCl} \cdot 0.25 \text{ H}_2\text{O}$:

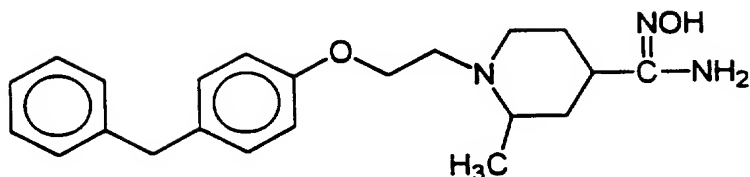
- 256 -

Calc: C, 70.38; H, 7.38; N, 7.46
Found: C, 70.10; H, 7.00; N, 7.35

Example 445

5

10



To a stirred solution of 250 mg of the compound of example 444 in 10 ml of absolute ethanol containing 500 mg of triethylamine is added 250 mg of $\text{NH}_2\text{OH}\cdot\text{HCl}$ and the mixture is heated to reflux and is allowed to reflux for $2\frac{1}{2}$ hours. The mixture is cooled to room temperature and is concentrated in vacuo to provide a crude oily gum, which is extracted with ethyl acetate. The organic extract is washed with water, dried over Na_2SO_4 and concentrated in vacuo to give a residue which is chromatographed on silica gel using 85% CHCl_3 , 14% ethanol, and 1% NH_4OH as eluant to provide 166 mg of the title compound, as white solid.

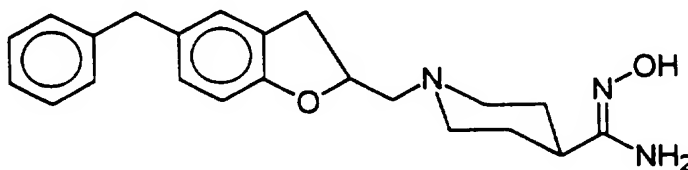
25 Calcd. for $\text{C}_{22}\text{H}_{29}\text{N}_3\text{O}_2 \cdot \frac{1}{4} \text{H}_2\text{O}$:

Calc: C, 71.03; H, 7.99; N, 11.30

Found: C, 71.28; H, 7.92; N, 11.16.

Example 446

30



35

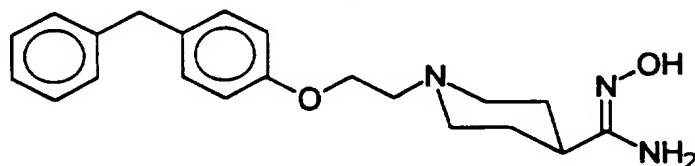
- 257 -

To a stirred solution of the product of Example 284 (1.5 g) and hydroxylamine hydrochloride (0.38 g, Aldrich) in ethanol (10 mL) was added sodium ethoxide (0.38 g) and the mixture heated to reflux for 4h and allowed to stand at room temperature for 2 days. The volatiles were removed and the residue chromatographed over silica gel using CHCl₃/Ethanol/Aqueous NH₃ 85/14/1, to give the title product as a colorless solid.

Anal. for C₂₂H₂₇N₃O₂

Calculated		Found
72.30	C	72.03
7.45	H	7.54
11.50	N	11.21

Example 447

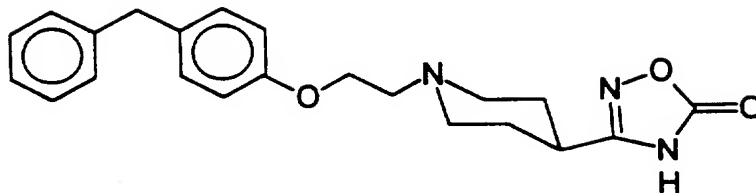


The procedure of Example 446 was repeated using the product of Example 441 in the place of the product of Example 284 to give the title product as a colorless solid.

Anal. for C₂₄H₃₁N₃O₄. 0.25 H₂O

Calculated		Found
67.03	C	67.01
7.38	H	6.98
9.77	N	9.43

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Example 448

To a stirred solution of the product of Example 447 (0.45 g) in THF (10 mL at -60°C was added a toluene solution of phosgene (0.931 M, 3.3 mL, Fluka). The mixture was allowed to warm to room temperature over 16 hr. The volatiles were removed and the residue chromatographed over silica gel using CHCl₃/Ethanol/Aqueous NH₃ 25/10/1, to give the title product as a colorless hygroscopic solid.

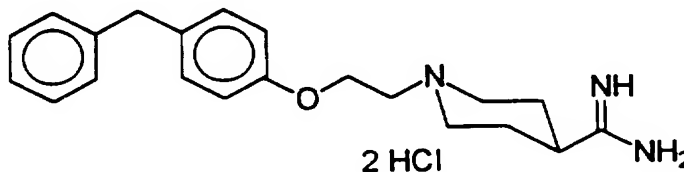
10

15

Anal. for C₂₂H₂₅N₃O₃ · 0.5 H₂O

Calculated			Found
68.02	C		68.00
6.75	H		6.54
10.82	N		10.89

20

Example 449

A solution of the product of Example 447 (0.576 g) in ethanol (15 mL) and acetic acid (3 mL) was hydrogenated in a parr hydrogenation apparatus over 4% Pd/C under 60 psi of hydrogen pressure for 24 hr. The solution was filtered and the filtrate concentrated. The residue was chromatographed over reverse phase silica gel using

35

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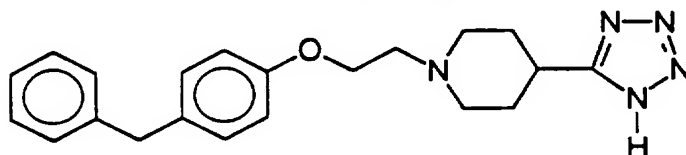
methanol/water as eluant of provide the free base of the title product. This material was taken in a small volume of ethanol and saturated ethanol HCl was added. The mixture was concentrated. The residue was dried at 78°C/0.5mm to give the title compound as a sticky solid.

Anal. for $C_{21}H_{27}N_3O \cdot 1.9 HCl \cdot 0.75 H_2O$

10	Calculated		Found
	60.02	C	59.99
	7.29	H	7.18
	10.00	N	9.50
15	16.03	Cl	16.12

Example 450

20



The product from Example 441 (350 mg) was dissolved in xylene (15 ml) and was treated with NaN_3 (220 mg), tributyltin chloride (0.38 ml) and LiCl (140 mg), and the mixture was heated to reflux under nitrogen atm. and was allowed to reflux for 20 hours. The mixture was cooled to room temperature and concentrated in vacuo to afford an oily gum which was taken up in methanol (~20 ml) and filtered. The filtrate was concentrated in vacuo to provide an oily gum which upon reverse phase column chromatography yielded 182 mg of the title compound as white solid.

35 Calculated for $C_{21}H_{25}N_3O \cdot 0.6 H_2O$:

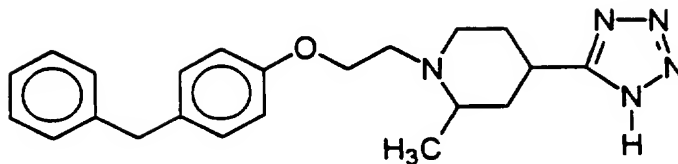
Calc: C, 67.39; H, 7.06; N, 18.71.

Found: C, 66.97; H, 6.87; N, 19.10.

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Example 451

5



Following the procedure described in Example 450, and
10 replacing the product of Example 441, with the product
of Example 444, provided the title compound as white
solid.

Calculated for $C_{22}H_{27}N_5O \cdot H_2O$:

15 Calc:

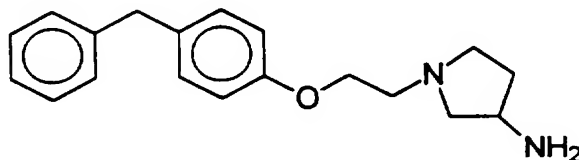
C, 66.81; H, 7.39; N, 17.71.

Found:

C, 67.12; H, 7.10; N, 17.63.

Example 452

20



25 The product from Example 256 (1.12g, 3.3 mmol) was
dissolved in 50 mL 1.2 N HCl and stirred at 100°C for
12 hours. The reaction was cooled to RT and made basic
with 10% NaOH. The aqueous phases was extracted with 5
X 40 mL ethyl acetate. The combined organic extracts
30 were dried (Na_2SO_4), filtered, and concentrated to
afford a brown oil. The product had the following
properties: Anal. calcd for $C_{19}H_{24}N_2O \cdot 0.70 H_2O$:

Calculated:

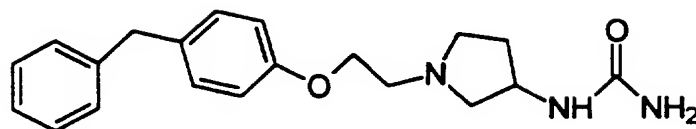
C, 73.85; H, 8.28; N, 9.07.

Found:

C, 73.79; H, 8.09; N, 8.84.

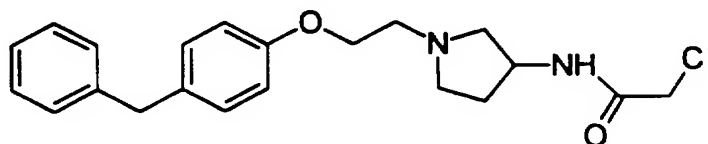
35

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Example 453

SC-57244

The product from Example 452 (645mg, 2.16 mmol) and
10 trimethylsilylisocyanate (364mg, 3.16 mmol) were
dissolved in 10 mL THF. The reaction was stirred for
12 hours at RT under argon. The reaction was quenched
with 10 mL methanol. The solvent was concentrated in
vacuo and the residue was dissolved in 20 mL methylene
15 chloride. The organic phases was washed with 3 X 20 mL
water and dried (Na_2SO_4) to afford the crude product as
a tan solid. The solid was recrystallized from
methanol/diethyl ether to give the pure product as a
tan solid. The product had the following properties:
20 mp 132-134°C. Anal. calcd for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_2 \cdot 0.10 \text{ H}_2\text{O}$: C,
70.40; H, 7.44; N, 12.31. Found C, 70.36; H, 7.47; N,
12.22.

Example 454

HCl

To a stirred solution of the amine from example 452
(100 mg, 0.34 mmol) in methylene chloride (1 ml) at
room temperature, chloroacetyl chloride (30 μmol , 1.1
35 eq) was added. The reaction mixture was stirred at
room temperature for 10 min, evaporated and the residue

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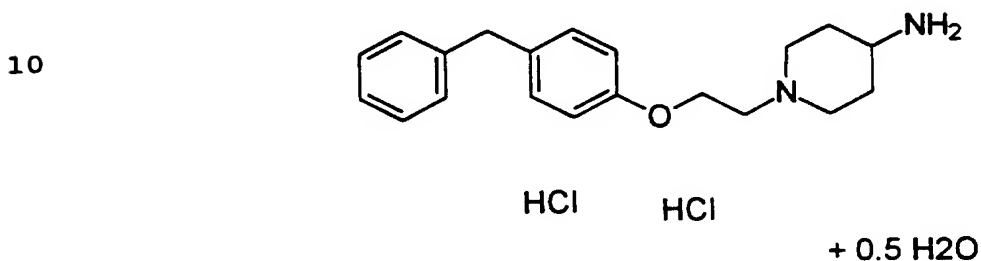
crystallized from diethyl ether to afford the title compound (111 mg)

Anal. calc. $C_{21}H_{25}N_2O_2Cl \cdot 0.25 H_2O$:

Calc: C, 60.80; H, 6.68; N, 6.75.

5 Found: C, 60.72; H, 6.38; N, 6.53.

Example 455



15

The title compound was prepared from the compound of example 238 (500 mg) in a manner identical to that described in example 452. This afforded the title compound as a white solid (401 mg)

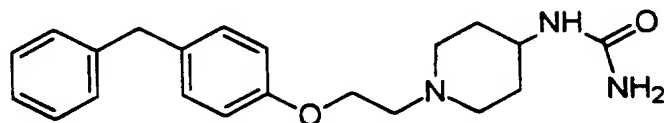
20 Anal. calc. $C_{20}H_{26}N_2O_2 \cdot HCl \cdot 0.5 H_2O$:

Calc: C, 61.22; H, 7.45; N, 7.14.

Found: C, 61.20; H, 7.50; N, 7.07.

Example 456

25



30 To a stirred solution of the amine from example 455 (180 mg, 0.47 mmol) and triethylamine (1 ml) in THF (4 ml) trimethylsilyl isocyanate (70 μ l, 1.5 eq) was added. The reaction mixture was stirred at room temperature for 3h, evaporated and the crude product

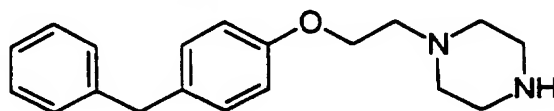
35 precipitated from diethyl ether to afford the title compound (175mg)

Anal. calc. $C_{21}H_{27}N_3O_2 \cdot 0.4 H_2O$:

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Calc: C, 69.93; H, 7.77; N, 11.65.

Found: C, 69.80; H, 7.69; N, 11.78.

Example 457

HCl

HCl

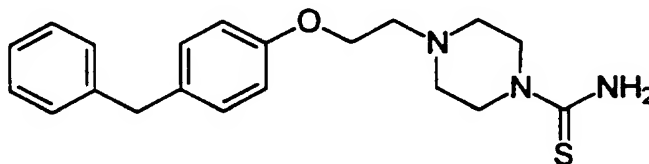
A mixture of the product of Example 277 and excess of 3 N HCl was heated on a steam-bath for 16 hr. The volatiles were removed in vacuo to provide the title compound as a white solid.

Anal. calc. for $C_{19}H_{24}N_2O \cdot 2HCl$

Calculated

Found

61.79	C	61.31
7.10	H	7.32
7.58	N	7.49
19.20	Cl	18.94

Example 458+ 0.25 H₂O

A mixture of the free base of the product of Example 457 (0.23 g), trimethylsilylisothiocyanate (0.81 mL, Aldrich), K₂CO₃ (100 mg) and toluene (5 mL) was heated to reflux for 16 hours. The mixture was concentrated

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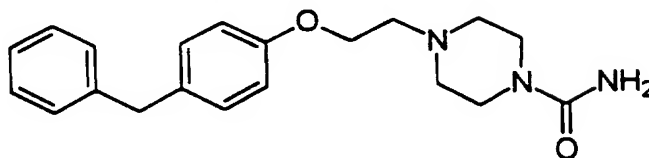
and the residue chromatographed on silica gel using CHCl₃/ethanol/aqueous NH₃, 85/14/1, to give the title product as a solid.

5 Anal. for C₂₀H₂₅N₃OS. 0.25 H₂O

Calculated			Found
66.73	C		66.87
7.14	H		6.91
11.67	N		11.65
8.91	S		8.88

Example 459

15



20

The procedure of Example 458 was repeated using trimethylsilyl isocyanate in the place of trimethylsilyl isothiocyanate to provide the title product as a solid.

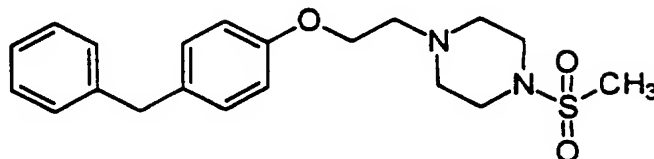
25

Anal. for C₂₀H₂₅N₃O₂

Calculated			
Found			
70.77	C		70.54
7.42	H		7.75
12.38	N		12.31

35

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Example 460

5

To a stirred solution of the free base of the product of Example 457 (0.33 g), and diisopropylethylamine (0.22 mL) in CH_2Cl_2 (5 mL) at -78°C was added methane sulfonylchloride (0.09 mL). The mixture was allowed to warm to room temperature over 1 hr. To the reaction mixture was added saturated aqueous NaHCO_3 and extracted with ethyl acetate. The organic extract was washed with water, dried over MgSO_4 and concentrated in vacuo. The residue was crystallized from CH_2Cl_2 to give the title product as a white solid as carbondioxide adduct.

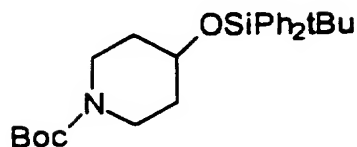
Anal. calc. for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{OS} \cdot \text{CO}_2$

20

Calculated			Found
60.27	C		60.18
6.26	H		6.62
6.69	N		6.65
7.66	S		7.80

25

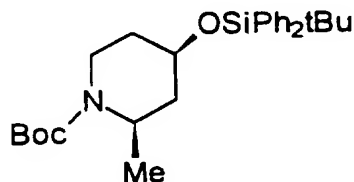
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Example 461

10 To a stirred solution of N-t-butyloxycarbonyl-4-hydroxypiperidine (3.00 g) and imidazole (2.7 g) in DMF (5 ml) at room temperature, t-butyldiphenylsilyl chloride (4.5 g) was added. The reaction mixture was stirred at room temperature overnight, quenched into water and the aqueous solution extracted into diethyl ether. The organic extracts were combined, dried

15 (Na_2SO_4) and evaporated to afford a clear oil. The crude product was purified by chromatography on silica (eluant, hexane/diethyl ether, 90/10) to afford the title compound (6.30 g)

20 Anal. calc. $\text{C}_{26}\text{H}_{37}\text{NO}_3\text{Si}$:
Calc: C, 71.03; H, 8.48; N, 3.19.
Found C, 71.26; H, 8.39; N, 2.76.

Example 462

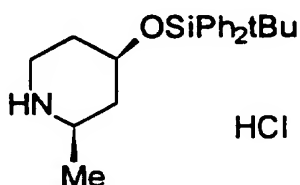
30

To a stirred solution of the product from example 461 (800 mg) in diethyl ether (5 ml) and TMEDA (1 ml) at -78° , sec butyl lithium was added. The reaction mixture was stirred at -78° for 3 hr and then quenched

35 with methyl iodide (1 ml) The reaction mixture was allowed to attain room temperature and then partitioned

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between diethyl ether and water. The organic layer was separated, dried (Na_2SO_4) and evaporated. The crude product was purified by chromatography on silica (eluant, hexane/diethyl ether, 75/25) to yield the title compound (650 mg).

Example 463

To a stirred solution of the product from example 462 (110 mg) in methylene chloride (1 ml) at room temperature, trifluoroacetic acid (2 ml) was added. The reaction mixture was stirred at room temperature for 10 mins, evaporated and the residue partitioned between diethyl ether and saturated potassium hydrogen carbonate solution. The organic layer was separated, dried (Na_2SO_4) and evaporated to afford a clear oil. The crude product was converted into its hydrochloride and crystallized from ethanol/diethyl ether to afford the title compound (40 mg)

Anal. calc. $\text{C}_{22}\text{H}_{31}\text{NOSi} \cdot \text{HCl} \cdot \text{H}_2\text{O}$:

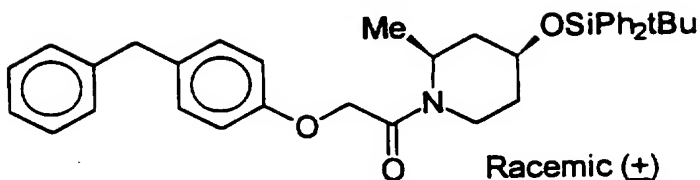
Calc: C, 64.76; H, 8.40; N, 3.43.

Found: C, 64.60; H, 7.97; N, 3.47.

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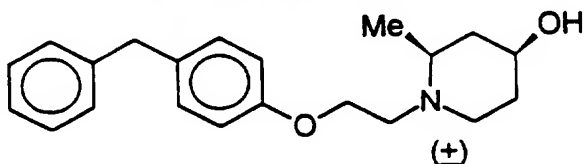
Example 464

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10 The title compound was prepared from the acid described in example 380 (1.89 mg) and the product from example 463 (2.3 g) in a manner analogous to that described in example 389. This afforded the title compound (2.55 g).

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Example 465

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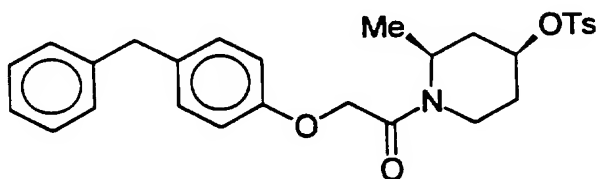
The title compound was prepared from the product of example 464 (2.5 g) in a manner identical to that described in example 397. This afforded the title compound (920 mg, 66%)

Anal. calc. $C_{21}H_{27}NO_2 \cdot 0.4 H_2O$:

Calc: C, 68.33; H, 7.86; N, 3.79.

Found: C, 68.45; H, 8.12; N, 3.74.

25

Example 466

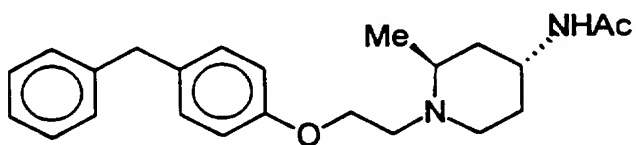
35

- 269 -

To a stirred solution of the product from example 464 (2.0 g) in THF (10 ml) at room temperature, TBAF (5 ml) was added. The reaction mixture was stirred at room temperature overnight, evaporated and the crude residue partitioned between ethyl acetate and saturated potassium hydrogen carbonate solution. The organic extracts were separated, dried (Na_2SO_4) and evaporated to afford the crude intermediate alcohol as a clear oil (1.80 g).

To a stirred solution of the above alcohol (1.8 g) in pyridine (10 ml) at 0°, toluene-4-sulfonyl chloride (800 mg) was added. The reaction mixture was stirred at room temperature for 24 h, evaporated and the residue partitioned between ethyl acetate and saturated potassium hydrogen carbonate solution. The organic extracts were separated, dried (Na_2SO_4) and evaporated to afford a yellow oil. The crude product was purified by chromatography on silica (eluant, diethyl ether) to afford the title compound (500 mg).

Example 467



To a stirred solution of the product from example 466 (400 mg 0.81 mmol) in DMF (5 ml) at 60°, sodium azide was added. The reaction mixture was stirred at 60° for 10 hr, evaporated and the residue partitioned between diethyl ether and water. The organic extracts were dried (Na_2SO_4), and evaporated to afford the crude intermediate azide (210 mg). To a stirred solution of the above azide (210 mg,) in methanol (5 ml) over a hydrogen atmosphere, 5% Pd/C was added. The reaction

- 270 -

5 mixture stirred at room temperature for 1 hr,
evaporated and the residue suspended/dissolved in ethyl
acetate. The organic solution was filtered (to remove
the catalyst) and evaporated to afford the intermediate
amine (150 mg). To a stirred suspension of lithium
aluminum hydride (50 mg) in THF (4 ml) at room
temperature the above amine was added. The reaction
mixture was stirred at room temperature for 30 mins,
quenched with water (200 mg) and then diluted with
10 ethyl acetate (20 ml). The reaction mixture was
filtered and the filtrate evaporated to afford the
intermediate diamine (80 mg). To a stirred solution of
the above diamine (70 mg) in acetic anhydride (1 ml) at
room temperature, pyridine (3 drops) was added. The
15 reaction mixture was stirred at room temperature for 15
mins, quenched with saturated sodium hydrogen carbonate
solution and extracted into ethyl acetate. The organic
extracts were dried (Na_2SO_4), evaporated, and the crude
product was precipitated from diethyl ether to afford
20 the title compound (62 mg).

Anal. calc. $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_2$.

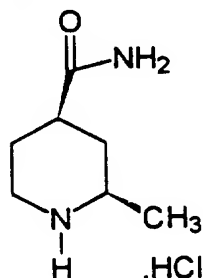
Calculated: C, 75.38; H, 8.25; N, 7.64.

Found: C, 76.05; H, 8.89; N, 6.70.

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Example 468

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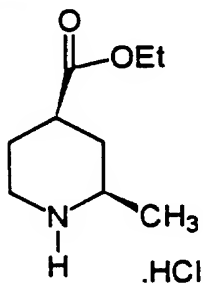


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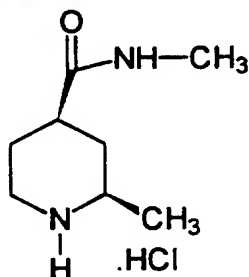
To a stirred solution of 100 ml of CH_2Cl_2 and 100
ml of 15M NH_4OH solution is added 10.0 g of 2-chloro-6-

- 271 -

methy1-4-pyridinecarbonyl chloride, and the mixture is stirred at room temperature for 30 minutes, during which time white solid is precipitated out of the mixture which is filtered and dried to provide 7.8 g of white solid. A solution of 5.5 g of the white solid in 55 ml of ethanol is exposed to hydrogen gas in parr bomb at 140°C at 1000 psi pressure for 18 hours. The mixture is cooled to room temperature. The catalyst is removed by filtration and the filtrate is concentrated in vacuo to provide 5.4 g of title compound as white crystalline solid.

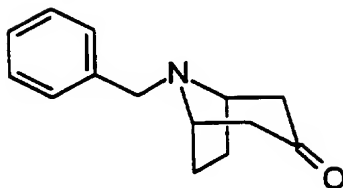
Example 469

Following the procedure described in example: 468 and replacing NH_4OH with ethanol provides the title compound.

Example 470

Following the procedure described in example: 468 and replacing NH_4OH with 40% CH_3NH_2 provides the title compound.

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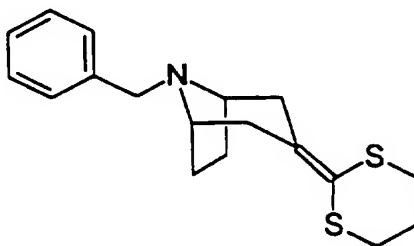
Example 471

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To a stirred suspension of nor-tropinone hydrochloride (REF) (9.2 g) in DMF (100 mL) at 0°C was added K₂CO₃ (10 g). After 5 min., benzyl bromide (7 mL) was added and the mixture allowed to warm to room temperature over 16 hr. The mixture was extracted with ethyl acetate and water. The organic phase was washed four times with water, dried over MgSO₄, and concentrated. The residue was chromatographed over silica gel using CHCl₃ containing 0.5% ethanol and a trace of aqueous NH₃ to give the title product as a colorless thick liquid (12.8 g).

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Example 472

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To a stirred solution of trimethylsilyldithiane (9.2 mL, Aldrich) in THF (175 mL) at 0°C was added in drops, n-butyl lithium (30.3 mL, 1.6 M cyclohexane solution). After 45 min., the product of Example 471 (12.8 g) in THF (20 mL) was added in drops. After 20 min., water and ether were added to the reaction mixture. The organic phase was dried over MgSO₄ and concentrated to give the title compound as a thick foul smelling liquid (15.52 g).

30

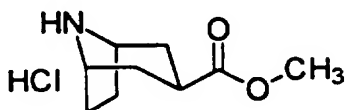
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Example 473

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To a stirred solution of the product of Example 472 (15.52 g) in methanol (480 mL) was added aqueous HCl (6 N, 20.4 mL), HgCl₂ (28 g) and trifluoro acetic acid (9.5 mL). The mixture was heated to reflux for 3 hr. The mixture was filtered through celite. The filtrate was concentrated and the residue chromatographed using CHCl₃/Ethanol/aqueous NH₃, 100/5/0.1, as eluant to provide the title compound as a thick liquid.

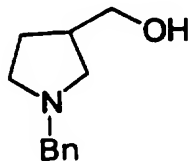
Example 474

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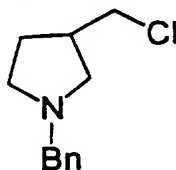
A solution of the product of Example 473 in methanol and Conc. HCl (2 mL) was shaken in a parr hydrogenation apparatus over 40% Pd(OH)₂/C under 60 psi hydrogen pressure at room temperature. After the uptake of hydrogen ceased, the solution was filtered and the filtrate concentrated in vacuo to give the title product.

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Example 475

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Methyl-1-benzyl-5-oxo-3-pyrrolidine carboxylate (25g, 0.11 mol) was dissolved in 200 mL THF under argon. Lithium aluminum hydride (6.5g, 0.17 mol) was added slowly to the THF. After the addition was complete, the reaction was refluxed for 3 1/2 hours. The reaction was cooled to RT and quenched with water/diethyl ether. After filtering and concentrating in vacuo, the crude product was obtained as a yellow oil. The oil was chromatographed (silica gel, methanol/methylene chloride/ammonium hydroxide 5/94/1) to afford the pure product as a yellow oil. The product had the following properties: Anal. calcd for $C_{12}H_{17}NO \cdot 0.10 H_2O$: C, 74.75; H, 8.98; N, 7.25. Found C, 74.66; H, 9.35; N, 7.20.

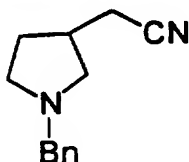
Example 476

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The product from Example 475 (0.46 g, 2.4 mmol) and thionyl chloride (1.5 mL, 20.6 mmol) were refluxed in 5 mL chloroform for 2 hours. The reaction was concentrated in vacuo, and the residue was dissolved in 20 mL water. 10% NaOH was added until the pH was ~8. The aqueous phase was extracted with 5 X 30 mL ethyl acetate. The combined organic phases were dried (Na_2SO_4), filtered and concentrated in vacuo to afford the chloride as an amber oil. The product had the

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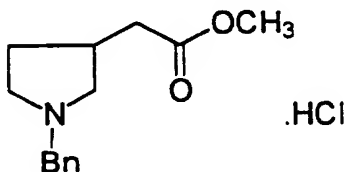
following properties: Anal. calcd for $C_{12}H_{16}NCl \cdot 0.20 H_2O$:
C, 67.57; H, 7.75; N, 6.57; Cl, 16.62. Found C, 67.57;
H, 7.44; N, 6.48; Cl, 16.47.

5

Example 477

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The product from Example 476 (2.52 g, 12 mmol),
sodium cyanide (3 g, 61 mmol) and aliquot 336 (156 mg,
0.38 mmol) were stirred in 5 mL water at 100°C for 48
15 hours. The reaction was cooled to RT and poured into
50 mL water. The aqueous phase was extracted with 4 X
40 mL ethyl acetate. The combined organic extracts
were dried (Na_2SO_4), filtered and concentrated to afford
the crude product as a dark yellow oil. The oil was
20 chromatographed (silica gel, methanol/methylene
chloride/ammonium hydroxide 1/98.5/0.5) to give the
pure product as a yellow oil. The product had the
following properties: Anal. calcd for $C_{13}H_{16}N_2 \cdot 0.08 H_2O$:
C, 77.40; H, 8.07; N, 13.89. Found C, 77.46; H, 8.37;
25 N, 13.84.

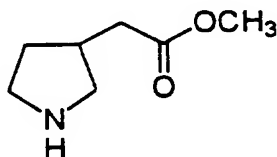
Example 478

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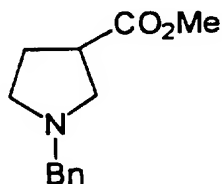
The product from Example 477 (1.08 g, 5.4 mmol)
35 was dissolved in 50 mL methanol and cooled to 0°C.
Acetyl chloride (25 mL, 35 mmol) was added slowly to
the methanol. The reaction was stirred at RT for 12

- 276 -

hours. The solvent was concentrated in vacuo, and the residue was dissolved in 10 mL water. To the water was added 25 mL saturated sodium bicarbonate. The aqueous phase was extracted with 4 X 50 mL ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to afford the crude ester as a yellow oil. The HCl salt was prepared by dissolving the ester in 5 mL diethyl ether and adding 3M ethanolic HCl dropwise. The pure HCl salt was obtained as a yellow oil. The product had the following properties: Anal. calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_2\text{Cl} \cdot 0.65 \text{ H}_2\text{O}$: C, 59.74; H, 7.63; N, 4.98. Found C, 59.68; H, 7.75; N, 5.05.

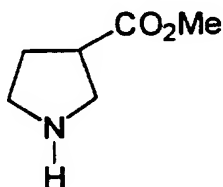
Example 479

The product from Example 478 (1.04 g, 3.8 mmol) and 1,4-cyclohexadiene (5 mL, 52 mmol) were dissolved in 20 mL methanol. The reaction flask was flushed with argon and 10% Pd/C (1.02 g) was added portionwise. The reaction was refluxed for 12 hours under argon. The reaction was filtered through Celite/silica gel. The solvent was concentrated in vacuo to afford the product as a yellow waxy solid. The product had the following properties: H.R.M.S. M+1 calcd for $\text{C}_7\text{H}_{13}\text{NO}_2$: 144.1025. Found 144.1011.

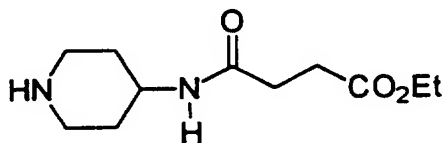
Example 480

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To a solution of N-benzyl-N-(trimethylsilylmethyl)-aminoacetonitrile (7.6 g, 32.7 mmol) and methyl acrylate (3.0 mL, 33.3 mmol) in CH₃CN (60 mL) was added AgF (4.5 g, 35.5 mmol) and the mixture stirred in the dark at 25°C for 19 h. The mixture was filtered and concentrated. Flash chromatography using a gradient of 10:1 to 3:1 hexane/EtOAc provided the title compound (3.3 g, 46%) as a colorless oil.

Example 481

The product from Example 480 (3.3 g, 15 mmol) was submitted to 60 psi H₂ in a Parr shaker in EtOH with catalytic Pd(OH)₂ at 25°C for 3 h. The solution was filtered and concentrated to provide the title compound.

Example 482

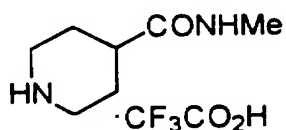
To a stirred solution of 2.28 g of BOC-isonipecotic acid in 10 ml of N,N-dimethylformamide was placed 2.56 g of N,N-disuccinimidyl carbonate and 2 ml of pyridine. The mixture was treated with 20 mg of N,N-4-dimethylamino pyridine and 1.0 g of triethylamine. The reaction mixture was stirred at

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room temperature under nitrogen atmosphere for 40 minutes. 1.53 g of β -alanine ethyl ester hydrochloride was added to the mixture. The mixture was stirred at room temperature for 16 hrs. The mixture was poured
5 into water and extracted with ethyl acetate. The organic extract was washed with a saturated solution of KHCO_3 , and water and saturated solution of KHSO_4 (KHCO_3 or KHSO_4) and dried over Na_2SO_4 . The solvent was removed by evaporation under reduced pressure to give crude
10 oily gum which was taken up in 10 ml of 90% trifluoroacetic acid and was allowed to stir at room temperature for 30 minutes. The solvent was removed by evaporation under reduced pressure to give 1.6 g of title compound which was used in Example 249 without
15 further purification.

Example 483

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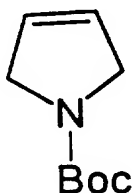


Following the procedure described in example 482
25 and replacing β -alanine ethyl ester hydrochloride with 40% methylamine provided the title compound as TFA salt which was taken up to the next step without further purification.

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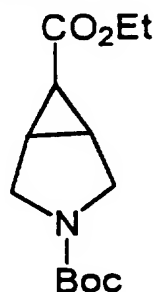
Example 484

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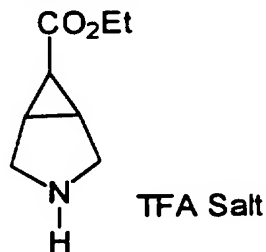


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3-Pyrroline (6.91 g, 100 mmoles) was dissolved in 150 ml of 80:20 mixture of dioxane:H₂O and was treated with 25 ml of Et₃N and the mixture was stirred at room temperature for 10 minutes. Di-tert-butyl dicarbonate (18.6 g, 100 mmoles) was added and the mixture was stirred at 25°C for 6 hours. The mixture was concentrated in vacuo to yield oily residue, which was dissolved in ethyl acetate (~100 ml), and was washed with water, dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo to provide 8.6 g. The title compound whose H¹ NMR 300 MHz spectrum was consistent with proposed structure.

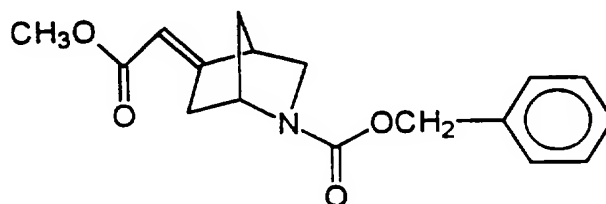
Example 485

The compound was prepared following the methodology described in European patent EP 0 413 455 A2 and replacing 1-benzyloxycarbonyl-3-pyrroline with the product from Example 484. H¹ NMR 300 MHz spectrum was consistent with proposed structure.

Example 486

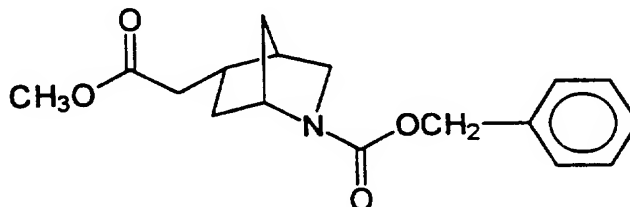
- 280 -

The product from Example 485 (1 g) was taken up in 20 ml of CH_2Cl_2 and was treated with 2 ml of TFA and the mixture was stirred at room temperature for 3 hours. The mixture was concentrated in vacuo to provide 1.15 g of title compound as oil whose ^1H NMR 300 MHz spectrum was consistent with proposed structure.

Example 487

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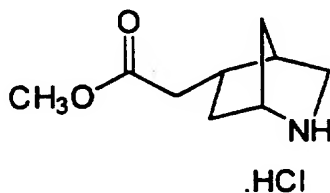
A solution of 2.4 g of 2-(carbobenzyloxy) 2-azabicyclo[2.2.1]heptan-5-one (J. Med. Chem. 1992, 35, 2184-2191), 6.7 g of methyl (triphenylphosphoranylidene) acetate (Aldrich), 25 mL toluene and 10 mL THF was refluxed for 14 hours under N_2 . The reaction mixture was cooled, concentrated and purified on a silica gel column eluting with 30% ethyl acetate in hexane to yield 2.31 g of a tinted liquid. The NMR spectra was consistent for the proposed structure.

Example 488

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- 281 -

A mixture of 2.3 g of the product from example 487, 1.8 g of magnesium turnings, and 80 mL of anhydrous methanol was stirred under N₂ with cooling in a water bath until all of the metal had dissolved (~4h). A 100 mL portion of 3N HCl was added and stirred for 5 minutes and then concentrated to a volume of approximately 50 mL. The aqueous residue was extracted thoroughly with ether, the organic extracts concentrated and the residue purified on a silica gel column eluting with 40% ethyl acetate in hexane to yield 1.4 g of colorless liquid. The NMR spectra was consistent for the proposed structure.

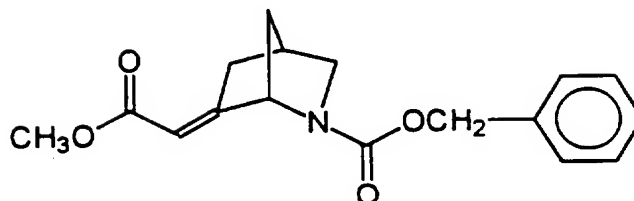
Example 489

A solution of 1.3 g of the product from example 488 and 4.5 mL of 1N HCl in 50 mL of methanol was decarbobenzyloxyated under an atmosphere of hydrogen using 50 mg of 5% palladium on carbon catalyst at room temperature for 16 hours. The reaction mixture was filtered through a pad of celite and the filtrate concentrated. The residue, 700 mg, was used directly in the next step without further purification. The NMR spectra was consistent for the proposed structure.

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Example 490

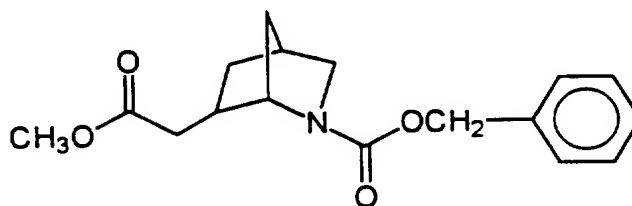
5



10 A solution of 4.9 g of 2-(carbobenzyloxy)-2-azabicyclo[2.2.1]heptan-6-one (J. Med. Chem. 1992, 35, 2184-2191) in 75 mL of toluene was reacted with 10.0 g of methyl (triphenylphosphoranylidene) acetate (Aldrich) as described in Example 487. The reaction was worked up and purified in the same manner to
15 produce 6.9 g of colorless oil. The NMR spectra was consistent for the proposed structure.

Example 491

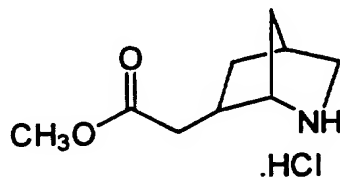
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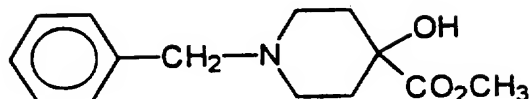
A mixture of 6.7 g of the product from example 490, 5.4 g of magnesium turning and 500 mL of anhydrous methanol was reacted as described in Example 488. The product was isolated as previously described to afford
30 5.0 g of viscous oil. The NMR spectra was consistent for the proposed structure.

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Example 492

10 A 1.4 g quantity of product from example 491 was decarbobenzyloxylated as described in Example 489. The product was isolated as previously described to yield 1.0 g of white solid. The NMR spectra was consistent for the proposed structure.

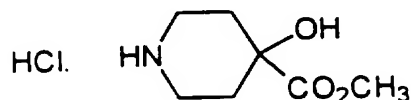
- 284 -

Example 493

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A mixture of 3.0 g of N-benzyl-4-piperidone (Aldrich), 2.0 g of trimethylsilylcyanide (Aldrich), 64 mg of zinc iodide and 20 mL of CH_2Cl_2 was refluxed for 18 hours under N_2 . The reaction mixture was cooled and blown down under N_2 and then concentrated in vacuo. The residue was dissolved in 7 mL of concentrated hydrochloric acid and stirred at room temperature for 30 hours. The reaction mixture was then concentrated to dryness and the residue repeatedly azeotroped with toluene and then dried in vacuo. The residue was dissolved in 75 mL of methanol and anhydrous HCl gas was bubbled into the solution for 1 hour with chilling in an ice bath. The excess HCl was removed by bubbling N_2 through the solution and then the reaction mixture was concentrated and partitioned between 10% K_2CO_3 solution and ethyl acetate. The aqueous portion was extracted several times with ethyl acetate and the combined organic extracts were concentrated and purified on a silica gel column eluting with 97.5% CHCl_3 -2.0% CH_3OH -0.5% NH_4OH to afford 1.5 g of white solid. The NMR spectra was consistent for the proposed structure.

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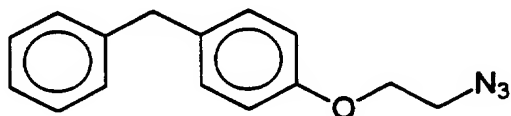
Example 494

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A mixture of 1.5 g of the product from example 493 in methanol containing excess dilute HCl solution was

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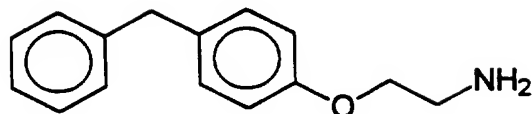
debenzylated using 20% palladium hydroxide on carbon at 5 psi for 20.6 hours at room temperature. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated. The residue was azeotroped several times with toluene and then dried in vacuo. The NMR spectra was consistent for the proposed structure.

Example 495

A mixture of 12.0 g (31.4 mmol) of tosylate described in example 186, 3.2 g (50.1 mmol) of sodium azide and 100 mL of DMF were heated at 60°C for 5 hours under N₂. The reaction mixture was cooled and partitioned between water and ether. The aqueous portion was extracted several times with ethyl acetate and the combined organic extracts were washed with saturated sodium chloride solution and dried over sodium sulfate, filtered and the filtrate concentrated to afford 8.5 g of golden liquid which was used without further purification.

NMR (CDCl₃) δ 3.47 (t, 2H), 3.89 (s, 2H), 4.03 (t, 2H), 6.8-7.3 (complex band, 9H).

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Example 496

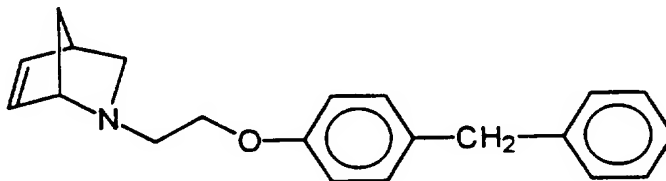
5

In a flame dried flask under N₂ was made a suspension of 2.30 g (60.6 mmol) of lithium aluminum hydride in 100 mL of anhydrous ether. The mixture was stirred and chilled to -70°C while a solution of 8.5 g (33.6 mmol) of the azide from example 495 in 50 mL of anhydrous ether was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. The reaction was then quenched by careful addition of 2.3 mL water, 2.3 mL of 15% aqueous sodium hydroxide solution, and 6.9 mL of water. The white suspension was stirred for 30 minutes, filtered, and the filtrate concentrated to produce 6.40 g of viscous oil which solidified upon chilling.

20

NMR (CDCl₃) δ 3.92 (t, 2H), 3.90 (s, 2H), 3.04 (t, 2H), 1.48 (broad band, 2H), 6.8-7.3 (complex band, 9H).

25

Example 497

30

In a Parr bottle was placed 568 mg of 1,3 cyclopentadiene, 704 mg of 37% aqueous formaldehyde solution, 1.5 g of amine from example 496 and 6.6 mL of 1N HCl. The bottle was stoppered and the contents vigorously stirred at room temperature for 18 hours. The reaction mixture was partitioned between 2N NaOH

35

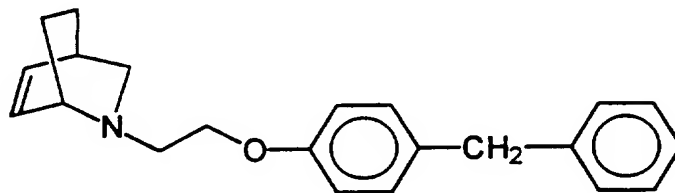
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solution and ethyl acetate. The aqueous portion was extracted several times with ethyl acetate and the combined organic extracts were washed with water, saturated NaCl solution, dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column eluting with 97.0% CH_2Cl_2 -2.5% CH_3OH -0.5% NH_4OH to afford 817 mg of product. m.p. 37-38°.

Anal. for $\text{C}_{21}\text{H}_{23}\text{NO} \cdot 0.05 \text{ H}_2\text{O}$

Calculated		Found
82.34	C	82.02
7.60	H	8.01
4.57	N	4.54

Example 498



In a Parr bottle was placed 801 mg of 1,3 cyclohexadiene, 819 mg of 37% aqueous formaldehyde solution, 2.0 g of amine from example 496 and 8.8 mL of 1N HCl. The bottle was stoppered and the contents vigorously stirred at 55° for 48 hours. The reaction was worked up and purified as described in Example 497 to yield 375 mg of a light brown viscous oil.

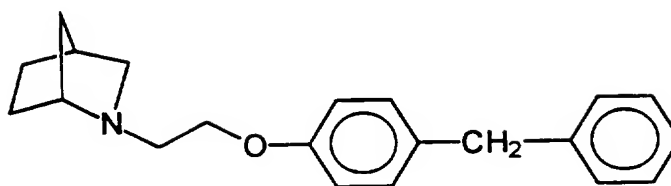
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Anal. for $C_{22}H_{25}NO \cdot 0.2 H_2O$

	Calculated		Found
	81.80	C	81.57
5	7.93	H	8.10
	4.34	N	4.51

Example 499

10



15

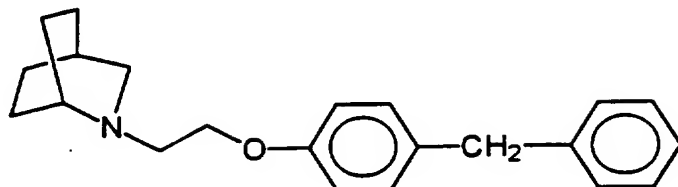
A solution of 171 mg of product from example 497 in ethanol was hydrogenated in a Parr shaker at room temperature and 5 psi for 1 hour using 4% palladium on carbon catalyst. The reaction mixture was filtered through a pad of celite, concentrated, and purified on a silica gel column eluting with 97.0% CH_2Cl_2 -2.5% CH_3OH -0.5% NH_4OH to yield 130 mg of viscous oil.

25

	Calculated		Found
	81.09	C	80.89
	8.23	H	8.42
	4.50	N	4.53

30

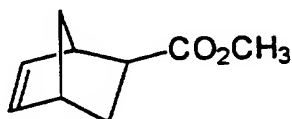
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Example 500

10 A solution of 133 mg of product from example 498 in ethanol was hydrogenated and purified as described in example 499 to afford 88 mg of oil.

Anal. for $C_{22}H_{27}NO \cdot 0.25 H_2O$

15	Calculated		Found
	81.06	C	80.77
	8.50	H	8.46
	4.30	N	4.21

Example 501

A mixture of 10 g of 5-norbornene-2-carboxylic acid (Pfaltz & Bauer), 11.1 g of K_2CO_3 , 12.1 g of methyl iodide (Aldrich) and 75 mL of DMF was stirred at room temperature for 18 hours. The reaction mixture was partitioned between ether and water and then the aqueous portion was extracted with ethyl acetate several times. The combined organic extracts were washed twice with saturated NaCl solution, dried over Na_2SO_4 , concentrated and the residue purified on a silica gel column eluting with 2.5% ethyl acetate in hexane to yield 6.2 g of a colorless sweet smelling

30

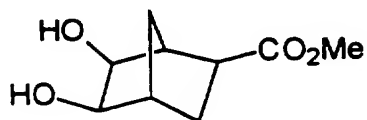
35

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liquid. The NMR spectra was consistent for the proposed structure.

Example 502

5



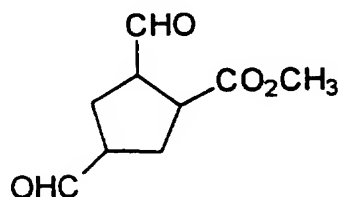
10

A mixture of 4.0 g of the product from example 501, 2.5 g of 4-methyl morpholine-N-oxide (Aldrich), 2 mL of a 2% solution of osmium tetroxide in isopropanol (Aldrich), 50 mL of water, and 50 mL of acetone was stirred under N₂ at room temperature for 18 hours. The reaction mixture was then partitioned between ethyl acetate and saturated NaCl solution and the aqueous portion was then extracted four times with additional ethyl acetate. The combined organic extracts were concentrated and the residue was purified on a silica gel column eluting with ethyl acetate to afford 4.6 g of a tan solid. The NMR spectra was consistent for the proposed structure.

25

Example 503

30



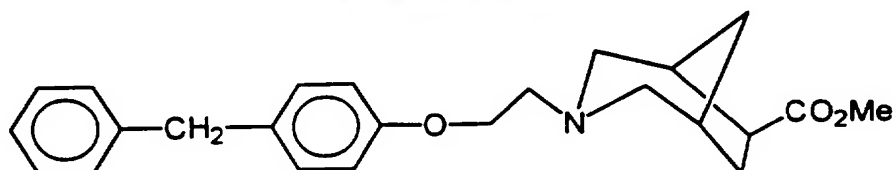
To a solution of 4.5 g of the product from example 502 in 100 mL of tert-butanol was added dropwise at room temperature a solution of 6.9 g of sodium periodate (Aldrich) in 25 mL of water. The resulting white suspension was stirred for 30 minutes and then

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filtered through a pad of celite. The filtrate was concentrated and the residue was purified on a silica gel column eluting with 80% ethyl acetate and 20% hexane to produce 1.6 g of a colorless liquid. The NMR spectra was consistent for the proposed structure.

Example 504

10



To a solution of 300 mg of amine hydrochloride from example 496 in 5 mL of methanol at 0° under N₂ was added 221 mg of the product from example 503 in 1 mL of methanol. The reaction was stirred for 5 minutes and then 126 mg of sodium cyanoborohydride (Aldrich) was added as a solid in portions over 10 minutes. The reaction was allowed to warm to room temperature, stirred overnight and then partitioned between 10% K₂CO₃ solution and ethyl acetate. The aqueous portion was extracted several additional times with ethyl acetate and the combined organic extracts were concentrated and purified on silica gel column eluting with 40% ethyl acetate in hexane to afford 190 mg of a colorless oil.

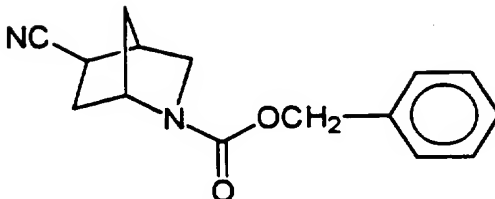
Anal. for C₂₄H₂₉NO₃

30	Calculated		Found
	75.96	C	75.62
	7.70	H	7.60
	3.69	N	3.59

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Example 505

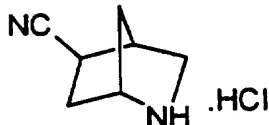
5



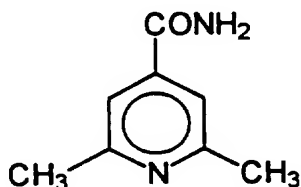
A solution of 3.0 g of 2-(carbobenzyloxy)-2-azabicyclo[2.2.1]heptan-5-one (J. Med. Chem. 1992, 35, 2184-2191) and 1.2 g of lithium cyanide (Johnson & Matthey) in 40 mL of dry THF was stirred at room temperature under N_2 . A solution of 6.0 g of diethylcyanophosphonate (Aldrich) in 10 mL of dry THF was then added in one portion and the reaction stirred for 30 minutes. The reaction was quenched with 100 mL of water and extracted with ethyl acetate several times. The combined organic extracts were washed with saturated NaCl solution, dried over Na_2SO_4 , and concentrated. The residue was azeotroped several times with toluene. This material was dissolved in 25 mL of dry THF and 1.2 mL of tert-butanol and added to 367 mL of a 0.1 M solution of samarium diiodide in THF (Aldrich) in one portion under N_2 at room temperature. The reaction was stirred for 1 hour and then quenched with 250 mL of 1N HCl and stirred for 15 minutes. The reaction was extracted several times with ethyl acetate and the combined organic extracts were washed with 5% aqueous $Na_2S_2O_3$ solution and then saturated NaCl solution, dried over Na_2SO_4 , and concentrated. The residue was purified on a silica gel column eluting with 40% ethyl acetate in hexane to afford 1.53 g of white solid. The NMR spectra was consistent for the proposed structure.

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Example 506

10 A 1.5 g quantity of the product from example 505. was decarbobenzyloxylated as described in example 489 to yield 1.0 g of salt. The NMR spectra was consistent for the proposed structure.

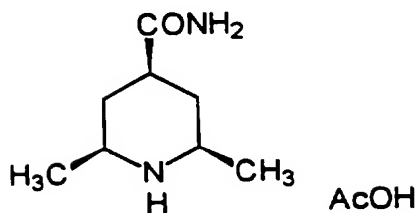
Example 507

20

To a stirred solution of 2,6-dimethyl-4-cyanopyridine, (3.0 g 22.5 mmol) (JACS, 81, 4004, (1959) in ethanol at 0°C (12 ml), 30% hydrogen peroxide (9 ml, 87.3 mmol) followed by NaOH (2.16 g, 54 mmol) were added. The reaction mixture was stirred at 0°C for 30 minutes, diluted with water (50 ml) and extracted into CHCl₃ (3 x 50 ml). The organic extracts were separated, dried (Na₂SO₄) and evaporated to afford the title compound (1.7 g, 50%).

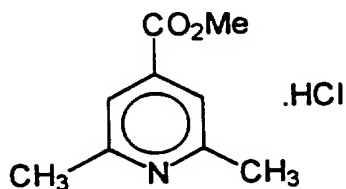
30

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Example 508

10 The compound of example 487 (950 mg)) was hydrogenated in a Parr shaker in EtOH (10 ml)/AcOH ($\frac{1}{2}$ ml) at 1200 psi and 140°C over 5% Ru/C catalyst for 24 hours. The reaction mixture was filtered, evaporated and the resulting solid precipitated from diethyl ether/ethanol to afford the title compound (480 mg)

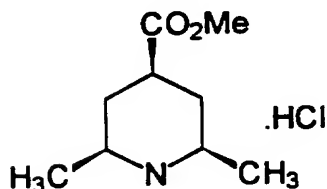
15 which was used as is in Example 316.

Example 509

25 To a stirred solution of the compound from Example 507 (800 mg, 5.3 mmol) in methanol (35 ml), HCl gas was introduced through a gas inlet tube for 35 minutes. The reaction mixture was evaporated in vacuo, to afford the title compound (1.38 g) as a white solid.

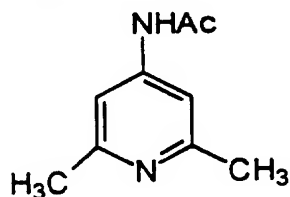
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Example 510

10 The title compound was prepared as described in Example 508, substituting the compound of Example 507 with that of 509.

The title compound was used as is in Example 317.

Example 511

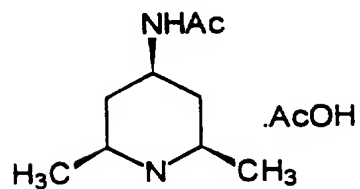
20

To a mixture of acetic anhydride (6 ml) and pyridine ($\frac{1}{2}$ ml), 4-amino-2,6-dimethylpyridine (1.0 g, 8.2 mmol) (Recueil 86, 655, (1967)) was added. The reaction mixture was stirred overnight, quenched with aqueous NaHCO_3 , and extracted into CHCl_3 (2 x 50 ml).
25 The organic extracts were dried (Na_2SO_4) and evaporated to afford an off white solid. The crude product was purified by chromatography on silica (eluant, $\text{CHCl}_3/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$, 85:14:1) to afford the title compound,
30 (520 mg).

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Example 512

5



10 The title compound was prepared as described in Example 508, substituting the compound of Example 507 with that of Example 511.

The title compound was used as is in Example 315.

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LTA₄ Hydrolase Methods

The following Table presents data demonstrating the pharmacological activity of the LTA₄ hydrolase inhibitors of the present invention having the formula I, Ar¹-Q-Ar²-Y-R-Z, as defined herein. One or more of three different assays, (1) an in vitro LTA₄ hydrolase enzyme assay, (2) a human whole blood assay utilizing calcium ionophore stimulation, and (3) a murine ex vivo assay utilizing calcium ionophore stimulation were employed to determine the level of LTA₄ hydrolase inhibitor activity.

Recombinant Human LTA₄ Hydrolase Assay for LTA₄ Hydrolase Inhibitor Activity

Compounds of the present invention were tested for LTA₄ hydrolase inhibitor activity against recombinant human LTA₄ hydrolase (rhLTA₄H). Recombinant human LTA₄ hydrolase-encoding vectors were prepared and used to express rhLTA₄H essentially as described by J. Gierse, et al., *Protein Expression and Purification*, 4, 358-366 (1993). Briefly, LTA₄ hydrolase encoding DNA was amplified by polymerase chain reaction using a pair of oligonucleotide primers based on the nucleotide sequence from the 5'-end, and the complement of the 3'-end, of the coding region of the LTA₄ hydrolase gene, the nucleotide sequence of which gene is known. (See, C. Funk, et al., *Proc. Natl. Acad. Sci. USA* 84, 6677-6681 (1987)). A λgt11 human placental cDNA library (Clontech, Palo Alto, CA) provided the nucleic acid template. The LTA₄ hydrolase encoding region had a length of about 1.9 kb. The amplified 1.9 kb DNA was isolated and cloned into the genomic baculovirus, *Autographa californica* nuclear polyderosis virus (AcNPV) DNA, and the baculovirus expression vector was transfected into *Spodoptera frugiperda* Sf-9 cells

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employing the calcium phosphase co-precipitation method (see, M. Summers, et al., *Tex. Agric. Exp. Stn. Bull.* 1555, 1-57 (1987)). Recombinant LTA₄ hydrolase enzyme was purified from the transfected Sf-9 cells
5 essentially as described by J. Gierse, et al., supra.

One or more predetermined amounts of a compound of the invention were incubated in assay buffer (0.1 M potassium phosphate, 5 mg/ml fatty acid free BSA, 10% DMSO, pH 7.4) for 10 minutes at room temperature with
10 250 ng of recombinant hLTA₄H to allow binding, if any, between the enzyme and inhibitor. The stock enzyme solution was 1 mg/ml LTA₄ hydrolase, 50 mM Tris, pH 8.0, 150 mM NaCl, 2.5 mM beta-mercaptoethanol, 50% glycerol. The specific activity of the enzyme was about 650
15 nMoles/min/mg. LTA₄ (i.e., substrate) was prepared from the methyl ester of LTA₄ (Biomol, Inc., Plymouth Meeting, PA) by treating the methyl ester with 30 molar equivalents of LiOH at room temperature for 18 hours. The LTA₄ substrate in its free acid form was kept frozen
20 at -80° C until needed. LTA₄ (free acid) was thawed and diluted in assay buffer (minus DMSO) to a concentration of 350 ng/ml and 25 µl (8 ng) of LTA₄ substrate was added to the reaction mixture (total volume of reaction mixture = 200 µl) at time zero. Each reaction was
25 carried out at room temperature for 10 minutes. The reaction was stopped by diluting 25 µl of the reaction mixture with 500 µl of the assay buffer without DMSO. LTB₄ was quantified in the diluted sample by a commercially available enzyme-linked immunoassay
30 [Caymen Chemical Co., Ann Arbor, MI] using the method recommended in the manufacturer's instructions and compared to the amount of LTB₄ produced in a negative control (i.e., essentially identical conditions except without addition of an inhibitor compound). The IC₅₀
35 was routinely calculated from the data produced.

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LTB₄ and Thromboxane Production by Calcium Ionophore Stimulated Human Blood for LTA₄ Hydrolase Inhibitor Activity

Human blood, collected in heparin-containing Vacutainer tubes, was diluted 1:4 with RPMI-1640 media and 200 μ l of the diluted blood was added into each of the wells of a 96-well microtiter plate. One or more concentrations of the leukotriene A₄ hydrolase inhibitor compounds being tested were prepared (diluted in DMSO) and 2 μ l added and gently mixed with the diluted whole blood. After incubating for 15 minutes at 37°C in a humidified incubator, calcium ionophore A23187 (Sigma Chemical Co., St. Louis, MO) was added to a final concentration of 20 mcg/ml and the incubation continued under the same conditions for an additional 10 minutes to allow LTB₄ formation. The reaction was terminated by centrifugation (833 g, 10 minutes at 4°C) and supernatant were analyzed for LTB₄ and thromboxane by commercially available enzyme-linked immunoassays (Caymen Chemical Co., Ann Arbor, MI) according to the manufacturer's instructions. The IC₅₀ of each test compound was determined from the amount of inhibition of LTB₄ production as compared to an essentially identical assay in which no inhibitor compound was present.

Ex Vivo LTB₄ and Thromboxane Production by Calcium Ionophore Stimulated Mouse Blood for LTA₄ Hydrolase Inhibitor Activity

Leukotriene A₄ hydrolase inhibitor compounds of the present invention were diluted to a predetermined concentration in phosphate buffered saline containing 2% DMSO and 1% Tween 80. The compounds were administered by oral gavage to adult male outbred mice weighing approximately 20-30 gm at a dose of 10 mg/kg body weight. (Compounds given at a dose of 50 mg/kg body weight are designated in following Table by the

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symbol, *.) Sixty (60) minutes after administration of an LTA₄ inhibitor compound of the invention, blood was collected (into heparin-containing tubes) from the retroorbital sinus. The heparinized blood was added to the wells of a microtiter plate along with an equal volume of RPMI-1640 media, and calcium ionophore A23187 was added to a final concentration of 20 mcg/ml. The mixture was incubated for 10 minutes at 37°C in a humidified incubator. The reaction was terminated by centrifugation (833 g, 10 minutes at 4°C). Supernatants were analyzed for LTB₄ and thromboxane by commercially available enzyme-linked immunoassays [Caymen Chemical Co., Ann Arbor, MI] in accordance with the manufacturer's instructions. The percent inhibition was determined by comparison to animals treated identically except that the solution administered by oral gavage was devoid of inhibitor compound.

20

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LTA₄ HYDROLASE INHIBITOR ACTIVITY

Ex. #	Recombinant Human LTA ₄ Hydrolase Assay IC ₅₀ LTA ₄ H	Inhibition of Calcium Ionophore- Induced LTB ₄ Production in Human Blood IC ₅₀ HWB	Murine Ex Vivo LTB ₄ Inhibition % I LTB ₄ /at 1 hour after administration of 10 mg/kg (* indicates administration of 50 mg/kg)
44	30 nM	79 nM	25%
45	26 nM	116 nM	35%
46	1.35 μM	1.5 μM	-
48	150 nM	390 nM	-
49	190 nM	490 nM	46%
62	30 nM	310 nM	-
63	40% at 25 μM	-	-
64	52% at 25 μM	-	-
65	110 nM	510 nM	-
66	220 nM	220 nM	-
67	11 nM	170 nM	0
68	480 nM	940 nM	-
69	6.52 μM	11.8 μM	-
70	35 nM	2.78 μM	-
71	6.5 μM	4.26 μM	-
76	2.9 μM	3.5 μM	-
112	7 nM	82 nM	82%*
113	1.23 μM	2.01 μM	-
114	3 μM	16 μM	-
115	60 nM	190 nM	-
116	53 nM	1.09 μM	18%
117	3.9 μM	4.15 μM	-
118	9 μM	-	-

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Ex. #	Recombinant Human LTA ₄ Hydrolase Assay	Inhibition of Calcium Ionophore- Induced LTB ₄ Production in Human Blood	Murine Ex Vivo LTB ₄ Inhibition
	IC ₅₀ LTA ₄ H	IC ₅₀ HWB	% I LTB ₄ /at 1 hour after administration of 10 mg/kg (* indicates administration of 50 mg/kg)
119	4 μ M	-	-
120	8 μ M	-	-
121	69 nM	360 nM	48%
122	77 nM	219 nM	57%
123	7 μ M	-	-
124	25 μ M	-	-
125	87 nM	260 nM	46%
126	630 nM	1.56 μ M	-
127	840 nM	2.48 μ M	-
128	70 nM	890 nM	74%
129	16 μ M	-	-
130	170 nM	1.01 μ M	-
131	4.3 μ M	25 μ M	-
132	84 nM	500 nM	83%
133	10 nM	43 nM	49%
134	33 nM	103 nM	63%
135	47 nM	91 nM	?
136	77 nM	72 nM	?
137	30 nM	80 nM	38%
138	420 nM	520 nM	21%
139	110 nM	580 nM	9%
140	60 nM	1.01 μ M	15%
141	13 nM	280 nM	-
142	37 nM	100 nM	32%
143	56 nM	290 nM	-

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Ex. #	Recombinant Human LTA ₄ Hydrolase Assay IC ₅₀ LTA ₄ H	Inhibition of Calcium Ionophore- Induced LTB ₄ Production in Human Blood IC ₅₀ HWB	Murine Ex Vivo LTB ₄ Inhibition % I LTB ₄ /at 1 hour after administration of 10 mg/kg (* indicates administration of 50 mg/kg)
144	80 nM	900 nM	-
147	1.06 μM	730 nM	94%
198	30 nM	310 nM	-
200	350 nM	1.9 μM	-
201	330 nM	1.75 μM	-
202	44% at 3 μM	-	-
203	380 nM	3.3 μM	-
204	49% at 25 μM	-	-
205	900 nM	1.15 μM	-
206	200 nM	1.65 μM	0
207	220 nM	640 nM	-
208	4 μM	2.15 μM	13%
209	3 μM	2.34 μM	0
210	4% at 25 μM	-	-
211	120 nM	620 nM	47%*
212	3 μM	3.28 μM	-
213	1.3 μM	4.65 μM	-
214	2.8 μM	10 μM	-
215	85 nM	190 nM	33%*
225	450 nM	1.86 μM	-
226	4% at 100 μM	-	-
227	210 nM	420 nM	23%
228	28% at 3 μM		-
229	240 nM	220 nM	70%
230	390 nM	284 nM	53%

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Ex. #	Recombinant Human LTA ₄ Hydrolase Assay IC ₅₀ LTA ₄ H	Inhibition of Calcium Ionophore- Induced LTB ₄ Production in Human Blood IC ₅₀ HWB	Murine Ex Vivo LTB ₄ Inhibition % I LTB ₄ /at 1 hour after administration of 10 mg/kg (* indicates administration of 50 mg/kg)
231	5 μ M	-	-
232	2.1 μ M	10 μ M	-
233	370 nM	490 nM	98%
234	8 μ M	-	-
235	10 μ M	-	-
236	20 μ M	-	-
237	450 nM	1.86 μ M	-
238	50 nM	180 nM	49%
239	9 μ M	-	-
240	1.07 μ M	2.45 μ M	33%
241	600 nM	630 nM	33%
242	132 nM	608 nM	95%
243	70 nM	650 nM	-
244	15% at 100 μ M	-	-
245	1.77 μ M	147 nM	97%
246	7 μ M	-	-
247	100 nM	200 nM	70%
248	200 nM	70 nM 605 nM	56%
249	3.2 μ M	429 nM	-
250	4.9 μ M	1.77 μ M	-
251	330 nM	733 nM	87%
252	160 nM	127 nM	94%
253	910 nM	490 nM	73%
254	6 μ M	1.26 μ M	87%
255	280 nM	608 nM	-

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Ex. #	Recombinant Human LTA ₄ Hydrolase Assay IC ₅₀ LTA ₄ H	Inhibition of Calcium Ionophore- Induced LTB ₄ Production in Human Blood IC ₅₀ HWB	Murine Ex Vivo LTB ₄ Inhibition % I LTB ₄ /at 1 hour after administration of 10 mg/kg (* indicates administration of 50 mg/kg)
256	210 nM	420 nM	23%
257	230 nM	1.32 μM	28%*
258	1.25 μM	1.44 μM	81%*
259	100 nM	440 nM	35%*
5 260	14% at 3 μM	-	-
261	1.25 μM	-	-
262	220 nM	2.48 μM	52%
263	4.5 μM	8.76 μM	60%
264	3 μM	1.10 μM	87%*
10 265	77 nM	450 nM	54%
266	6.5 μM	2.64 μM	29%
267	170 nM	580 nM	100%*
268	53% at 3 μM	7.98 μM	-
269	2.77 μM	1.18 μM	50%
15 270	50 μM	-	-
271	11 μM	7.98 μM	-
272	7 nM	76 nM	97%
273	610 nM	154 nM	100%
274	800 nM	1.25 μM	-
20 275	390 nM	146 nM	75%
276	4.1 μM	232 nM	75%
277	520 nM	546 nM	42%
278	22 nM	247 nM	95%
279	470 nM	410 nM	57%
25 280	11 nM	21 nM	33%
281	93 nM	167 nM	83%

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Ex. #	Recombinant Human LTA ₄ Hydrolase Assay	Inhibition of Calcium Ionophore- Induced LTB ₄ Production in Human Blood	Murine Ex Vivo LTB ₄ Inhibition
	IC ₅₀ LTA ₄ H	IC ₅₀ HWB	% I LTB ₄ /at 1 hour after administration of 10 mg/kg (* indicates administration of 50 mg/kg)
282	3.7 μ M	1.37 μ M	57%
283	19 nM	90 nM	90%
285	130 nM	1.73 μ M	-
286	41% at 100 μ M	-	-
287	330 nM	2.39 μ M	-
288	700 nM	960 nM	0
289	43 nM	316 nM	-
290	450 nM	528 nM	94%
291	8 μ M	1.85 μ M	67%
292	7 nM	52 nM	-
293	480 nM	3.2 μ M	93%
294	110 nM	340 nM	57%
295	440 nM	604 nM	80%
296	710 nM	512 nM	72%
297	120 nM	359 nM	63%
298	2.5 μ M	758 nM	-
299	57 nM	133 nM	93%
300	5 μ M	2.51 μ M	-
301	4.5 μ M	828 nM	81%
302	3 μ M	2.40 μ M	-
303	97 nM	1.65 μ M	-
304	15 nM	112 nM	80%
305	10 nM	1.23 μ M	42%
306	5 nM	177 nM	11%
307	440 nM		-

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Ex. #	Recombinant Human LTA ₄ Hydrolase Assay IC ₅₀ LTA ₄ H	Inhibition of Calcium Ionophore- Induced LTB ₄ Production in Human Blood IC ₅₀ HWB	Murine Ex Vivo LTB ₄ Inhibition % I LTB ₄ /at 1 hour after administration of 10 mg/kg (* indicates administration of 50 mg/kg)
309	2.5 μ M	1.77 μ M	96%
310	930 nM	1.35 μ M	96%
311	44% at 100 μ M	-	-
312	46% at 100 μ M	-	-
313	25 μ M	-	-
314	1.5 μ M	-	-
315	163 nM	648 nM	53%
316	50 nM	131 nM	85%
317			
318	2.5 μ M 4.2 μ M	-	-
319	47% at 100 μ M		
320	14 nM	354 nM	85%
321	250 nM	421 nM	87%
322	610 nM	154 nM	100%
323	800 nM	1.2 μ M	
324	220 nM	586 nM	62%
325	20 μ M	2.4 μ M	-
330	900 nM	90 nM	95%
331	16 nM	95 nM	97%
332	14 μ M	-	-
333	0.5 μ M 1.8 μ M	-	-
334	1 nM	N5Y	-
335	2 nM	115 nM	98%

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			Murine Ex Vivo LTB ₄ Inhibition
	Recombinant Human LTA ₄ Hydrolase Assay	Inhibition of Calcium Ionophore- Induced LTB ₄ Production in Human Blood	% I LTB ₄ /at 1 hour after administration of 10 mg/kg (* indicates administration of 50 mg/kg)
Ex. #	IC ₅₀ LTA ₄ H	IC ₅₀ HWB	
336	31 nM	187 nM	99%
337	360 nM	628 nM	82%
338 A	140 nM	690 nM	22%
5 338 B	8 nM	330 nM	92%**
338 C	34% at 3 μM	9.15 μM	-
339	2.0 μM	13.1 μM	47%
10 340 A	11 nM	74 nM	61%
340 B	120 nM	330 nM	64%
15 340 C	550 nM	730 nM	39%
341 A	5.7 μM	8.9 μM	-
341 B	140 nM	930 nM	29%
20 342	970 nM	2.12 μM	-
343	40% at 3 μM	-	-
344	? 11.1 μM	13.5 μM	-
345	35% at 3 μM	-	-
25 346 A	31% at 3 μM	-	-
346 B	1.9 μM	3.57 μM	23%
346 C	2.2 μM	6.69 μM	-
30 347 A	1.8 μM	7.05 μM	34%

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Ex. #	Recombinant Human LTA ₄ Hydrolase Assay	Inhibition of Calcium Ionophore- Induced LTB ₄ Production in Human Blood	Murine Ex Vivo LTB ₄ Inhibition
	IC ₅₀ LTA ₄ H	IC ₅₀ HWB	% I LTB ₄ /at 1 hour after administration of 10 mg/kg (* indicates administration of 50 mg/kg)
347 B	1.9 μM	5.7 μM	43%
347 C	5 nM	380 nM	52%
5 348 A	4.6 μM	5.7 μM	42%
348 B	440 nM	560 nM	22%
10 348 C	290 nM	540 nM	77%
349 A	480 nM	790 nM	78.5%
349 B	300 nM	320 nM	48%
15 349 C	13 nM	200 nM	52%
350 A	19 μM	13.6 μM	-
20 350 B	550 nM	950 nM	38%
350 C	620 nM	1.67 μM	35%
351 A	1.08 μM	2.72 μM	-
25 351 B	290 nM	2.05 μM	71%
351 C	43 nM	360 nM	42%
352	120 nM	1.34 μM	29%*
30 353	73 nM	260 nM	0
354 A	51% at 3 μM		-

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Ex. #	Recombinant Human LTA ₄ Hydrolase Assay	Inhibition of Calcium Ionophore- Induced LTB ₄ Production in Human Blood	Murine Ex Vivo LTB ₄ Inhibition
	IC ₅₀ LTA ₄ H	IC ₅₀ HWB	% I LTB ₄ /at 1 hour after administration of 10 mg/kg (* indicates administration of 50 mg/kg)
354 B	280 nM	600 nM	32%
354 C	480 nM	1.18 μM	6%
5 355 A	1.37 μM	2.23 μM	44%
355 B	870 nM	910 nM	37%
10 355 C	28 nM	210 nM	48%
356 A	350 nM	1.28 μM	14%
356 B	170 nM	750 nM	33%
15 356 C	100 nM	340 nM	48%
357 A	47 nM	790 nM	57%
20 357 B	730 nM	140 nM	60%
357 C	210 nM	420 nM	72%
357 D	40 nM	140 nM	-
25 358 A	1.55 μM	152 nM	-
358 B	410 nM	640 nM	33%
30 358 C	87 nM	590 nM	13%
359 A	100 μM	-	-

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Ex. #	Recombinant Human LTA ₄ Hydrolase Assay	Inhibition of Calcium Ionophore- Induced LTB ₄ Production in Human Blood	Murine Ex Vivo LTB ₄ Inhibition
	IC ₅₀ LTA ₄ H	IC ₅₀ HWB	% I LTB ₄ /at 1 hour after administration of 10 mg/kg (* indicates administration of 50 mg/kg)
359 B	10 μ M	-	-
359 C	3.5 μ M	4.2 μ M	-
5 360 A	36% at 100 μ M	-	-
360 B	19% at 100 μ M	-	-
10 360 C	5 μ M	-	-
361 A	24% at 100 μ M	-	-
361 B	7 μ M	-	-
15 362 A	5.07 μ M	3.35 μ M	28%
362 B	1.32 μ M	4.58 μ M	-
363	17 nM	57 nM	62%
20 364	36 nM	22 nM	77%
365	82 nM	336 nM	72%
369	42 μ M	1.53 μ M	100%
370	59 μ M	680 nM	96%
371	860 nM	650 nM	
25 375	900 nM	240 nM	67%
385	140 nM	210 nM	32%
386	32 nM	190 nM	51%
397	37 nM	120 nM	-
398	220 nM	470 nM	0
30 399	100 nM	220 nM	30%

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			Murine Ex Vivo LTB ₄ Inhibition
	Recombinant Human LTA ₄ Hydrolase Assay	Inhibition of Calcium Ionophore- Induced LTB ₄ Production in Human Blood	% I LTB ₄ /at 1 hour after administration of 10 mg/kg (* indicates administration of 50 mg/kg)
Ex. #	IC ₅₀ LTA ₄ H	IC ₅₀ HWB	
400	60 nM	380 nM	-
401	55 nM	170 nM	23%
402	20 nM	180 nM	58%
403	750 nM	3.8 μM	-
404	1.75 μM	2.75 μM	52%
405	420 nM	2.01 μM	49%
406	500 nM	4.0 μM	46%
407	20 μM	707 nM	0
408	76% at 100 μM	-	-
409	12 μM	-	-
410	33 μM	-	-
411	2.4 μM	-	-
412	190 nM	240 nM	72%
413	43 nM	42 nM	86%
414	11 μM	830 nM	-
415	5 μM	-	-
416	410 nM	1.97 μM	31%
417	4.3 μM	-	-
418	12 μM	-	-
419	47 nM	120 nM	90%
420	57 nM	133 nM	93%
421	410 nM	800 nM	-
422	100 nM	660 nM	37%
423	330 nM	700 nM	-
424	370 nM	850 nM	-

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Ex. #	Recombinant Human LTA ₄ Hydrolase Assay	Inhibition of Calcium Ionophore- Induced LTB ₄ Production in Human Blood	Murine Ex Vivo LTB ₄ Inhibition
	IC ₅₀ LTA ₄ H	IC ₅₀ HWB	% I LTB ₄ /at 1 hour after administration of 10 mg/kg (* indicates administration of 50 mg/kg)
425	16 nM	360 nM	60%
426	210 nM	403 nM	40%
427	350 nM	532 nM	68%
428	500 nM	6.6 μM	2%
429	250 nM	288 nM	80%
430	110 nM	290 nM	37%
431	140 nM	280 nM	71%
432	140 nM	630 nM	85%
433	18 nM	49 nM	71%
434	10 nM	63 nM	100%
435	225 nM	86 nM	-
436	720 nM	550 nM	-
437	113 nM	693 nM	-
438	3.2 μM	-	-
439	18 μM	-	-
440	30 nM	-	-
441	470 nM	410 nM	57%
444	300 nM	900 nM	-
445	330 nM	367 nM	-
446	35 nM	160 nM	70%
447	15 nM	292 nM	43%
448	820 nM	825 nM	-
449	140 nM	913 nM	-
450	240 nM	304 nM	91%
451	6 nM	?	90%
452	20 nM	290 nM	57%

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Ex. #	Recombinant Human LTA ₄ Hydrolase Assay IC ₅₀ LTA ₄ H	Inhibition of Calcium Ionophore-Induced LTB ₄ Production in Human Blood IC ₅₀ HWB	Murine Ex Vivo LTB ₄ Inhibition % I LTB ₄ /at 1 hour after administration of 10 mg/kg (* indicates administration of 50 mg/kg)
455	11 nM	180 nM	67%
456	87 nM	440 nM	72%
457	150 nM	620 nM	22%
458	560 nM	1.39 μM	-
459	1.11 μM	2.4 μM	44%
460	84 μM	-	-
465	300 nM	470 nM	38%
467	60 nM	226 nM	71%
496	10 nM	280 nM	54%
497	200 nM	216 nM	45%
498	56 nM	206 nM	22%
499	240 nM	220 nM	60%
500	140 nM	142 nM	53%
504	29 nM	7.7 μM	-

"-" means Not Determined

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We Claim:

1. A compound of the Formula I:



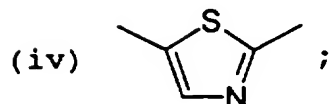
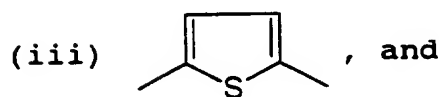
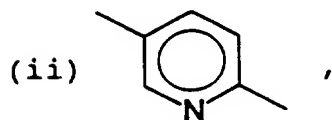
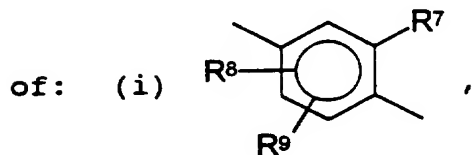
(I)

or a pharmaceutically acceptable salt thereof,
wherein:

Ar¹ is an aryl moiety selected from the group consisting of:

- (i) phenyl, mono-, di-, or tri-substituted phenyl with the substituents selected from the group consisting of Cl, Br, F, CF₃, lower alkyl, lower alkoxy, NH₂, NO₂ and OH;
- (ii) 2-, 4- or 5- thiazolyl,
- (iii) 2-, 3- or 4-pyridinyl,
- (iv) 2- or 3-thienyl, and
- (v) 2- or 3-furyl;

Ar² is an aryl moiety selected from the group consisting



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Q is selected from the group consisting of:

- (i) -O-,
- (ii) -CH₂-,
- (iii) -OCH₂-,
- (iv) -CH₂O-,
- (v) -NH-;
- (vi) -NHCH₂-,
- (vii) -CH₂NH-,
- (viii) -CF₂-,
- (ix) -CH=CH-,
- (x) -CH₂CH₂-, and
- (xi) carbon-carbon single bond;

Y is selected from the group consisting of

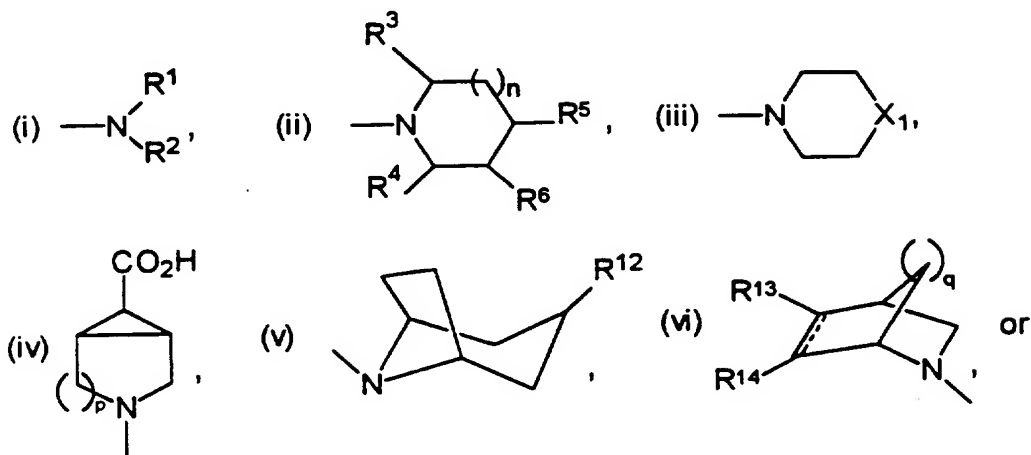
- (i) -O-,
- (ii) -S-,
- (iii) -NH-,
- (iv) -S(O)-, and
- (v) -S(O₂)-;

R is selected from the group consisting of:

- (i) linear or branched C₂-C₆ alkylenyl; or
- (ii) -C(R¹⁰)(R¹¹)-(CH₂)_m-; and

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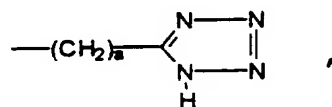
Z is selected from the group consisting of:



- (vii) a monocyclic or bicyclic heteroaromatic moiety having at least one heteroatom, wherein the heteroatom is nitrogen, and wherein the monocyclic heteroaromatic moiety comprises a 5- or 6-membered ring and the bicyclic heteroaromatic moiety comprises a fused 9- or 10-membered ring;

wherein R¹ and R² are independently selected from the group consisting of:

- (i) H,
(ii) lower alkyl or allyl,
(iii) benzyl,
(iv) $-(CH_2)_n-COR^{15}$,
(v)



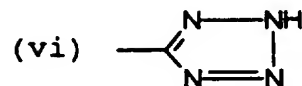
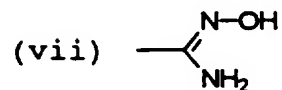
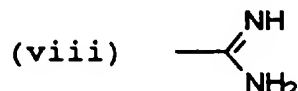
- (vi) $-(CH_2)_n-OH$;

R³ and R⁴ are independently H or lower alkyl;

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R^5 and R^6 are independently selected from the group consisting of:

(i) H,

(ii) -OH, =O or $-(CH_2)_4-OH$,(iii) $-(CH_2)_4-COR^{15}$,(iv) $-(CH_2)_4-CONH(CH_2)_6-CO_2R^{16}$,(v) $-NHR^{17}$,

R^7 is H, halogen, lower alkyl, lower alkoxy, nitro, hydroxy, or R^7 taken together with R^{10} is an alkylene group having one or two carbon atoms;

R^8 and R^9 are independently H, halogen, lower alkyl, lower alkoxy, NH_2 , NO_2 or OH;

R^{10} is H, lower alkyl, or R^{10} taken together with R^7 is an alkylene group having one or two carbon atoms;

R^{11} is H or lower alkyl;

R^{12} is selected from the group consisting of:

(i) H,

(ii) -OH or =O,

(iii) $-(CH_2)_4-COR^{15}$,(iv) $-(CH_2)_4-CONH(CH_2)_6-CO_2R^{16}$,(v) $-NHR^{17}$;

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R^{13} and R^{14} are independently hydrogen, $-(CH_2)_nCOR^{15}$, provided that at least one of R^{13} and R^{14} is hydrogen;

R^{15} is $-OR^{16}$, $-NHR^{16}$ or $-NHNH_2$;

R^{16} is H, lower alkyl or benzyl;

R^{17} is H, lower alkyl, benzyl, $-COR^{16}$ or $-CONH_2$;

X^1 is $\begin{array}{c} \diagup \\ NR^{18} \\ \diagdown \end{array}$, $-S-$, or $-O-$, wherein R^{18} is H, lower alkyl, $-CONH_2$, $-CSNH_2$, $-COCH_3$ or $-SO_2CH_3$;

a and b are independently integers of from 0 to 5;

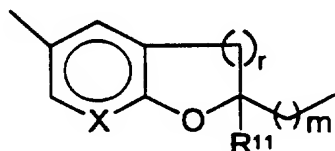
m is 1, 2 or 3;

n is 0, 1, 2 or 3;

p is 1 or 2; and

q is 1, 2 or 3;

provided however that where R is $-C(R^{10})(R^{11})-(CH_2)_m-$, and R^{10} taken together with R^7 forms an alkylenyl group having one or two carbon atoms, then $-Ar^2-Y-R-$ is

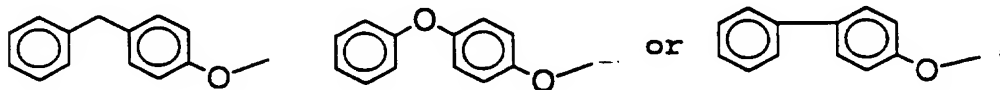


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wherein X is -CH- or -N-, and r is 1 or 2, further

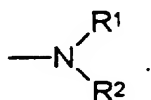
provided that wherein Z is $\text{—N} \begin{matrix} \text{R}^1 \\ \text{R}^2 \end{matrix}$ and either R¹ or R²,

or both R¹ and R² are $\text{—(CH}_2\text{)}_a\text{COR}^{15}$, then a is not 0;
and further provided that wherein Ar¹-Q-Ar²-Y- is



then (A) R¹ and R² are not simultaneously H or lower alkyl; or (B) R³, R⁴, R⁵ and R⁶ are not simultaneously H.

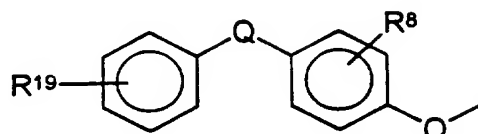
2. A compound according to Claim 1 wherein Z is an amine moiety of the formula



3. A compound according to Claim 2 wherein R¹ is H or lower alkyl and R² is $\text{—(CH}_2\text{)}_a\text{COR}^{15}$ wherein R¹⁵ is —OR^{16} , —NHR^{16} or —NHNH_2 .
4. A compound according to Claim 3 wherein a is 1, 2 or 3.
5. A compound according to Claim 4 wherein R¹⁵ is —OR^{16} or —NHR^{16} .
6. A compound according to Claim 5 wherein R¹⁶ is H.
7. A compound according to Claim 5 wherein R¹⁶ is methyl, ethyl or benzyl.

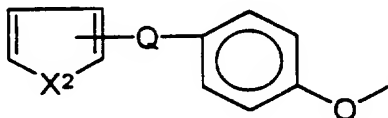
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8. A compound according to Claim 6 wherein R^{15} is $-OR^{16}$.
9. A compound according to Claim 6 wherein R^{15} is $-NHR^{16}$.
10. A compound according to Claim 7 wherein R^{15} is $-OR^{16}$.
11. A compound according to Claim 7 wherein R^{15} is $-NHR^{16}$.
12. A compound according to Claim 3 wherein R^{15} is $-NHNH_2$.
13. A compound according to Claim 3 wherein Ar^1-Q-Ar^2-Y- is



wherein Q is $-O-$, $-CH_2-$, $-CF_2-$ or $-CH_2O-$, R^8 and R^{19} are independently H, lower alkyl, lower alkoxy, halogen, NH_2 or NO_2 .

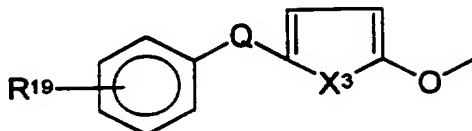
14. A compound according to Claim 3 wherein Ar^1-Q-Ar^2-Y- is



X^2 is $-S-$ or $-CH=N-$;
 Q is $-CH_2-$, $-CF_2-$, $-O-$ or $-CH_2O-$.

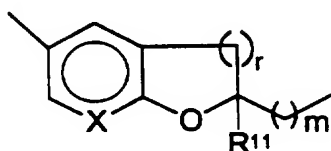
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15. A compound according to Claim 3 wherein
 $\text{Ar}^1\text{-Q-Ar}^2\text{-Y-}$ is



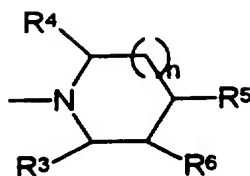
- X^3 is $-\text{S}-$, $-\text{CH}=\text{N}-$;
 Q is $-\text{CH}_2-$, $-\text{CF}_2-$, $-\text{O}-$ or $-\text{CH}_2\text{O}-$;
 R^{19} is H , lower alkyl, lower alkoxy, halogen,
 NH_2 or NO_2 .

16. A compound according to Claim 3 wherein $-\text{Ar}^2\text{-Y-R-}$
 is



17. A compound according to Claim 13 wherein
 Q is $-\text{CH}_2-$ or $-\text{O}-$, and
 R^{19} is hydrogen or fluorine.
18. A compound according to Claim 14 wherein Q is $-\text{CH}_2-$
 or $-\text{O}-$, and R^{19} is hydrogen or fluorine.
19. A compound according to Claim 15 wherein Q is $-\text{CH}_2-$
 or $-\text{O}-$, and R^{19} is hydrogen or fluorine.
20. A compound according to Claim 19 wherein
 X^3 is $-\text{CH}=\text{N}-$.
21. A compound according to Claim 18 wherein
 X^2 is $-\text{S}-$.
22. A compound according to Claim 1 wherein
 Z is

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wherein

R^3 and R^4 may independently be H or lower alkyl

R^5 and R^6 may independently be H, lower alkyl,

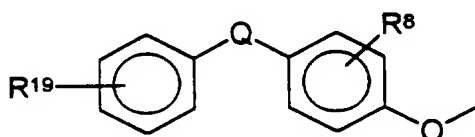
$-(CH_2)_nCOR^{15}$ or $-(CH_2)_nCONH(CH_2)_mCOR^{16}$

n is 0, 1, 2 or 3.

23. A compound according to Claim 22 wherein one of R^5 and R^6 is H and the other of R^6 and R^5 is $-(CH_2)_nCOR^{15}$.
24. A compound according to Claim 23 wherein n is 0, 1, 2 or 3.
25. A compound according to Claim 24 wherein R^{15} is $-OR^{16}$ or $-NHR^{16}$.
26. A compound according to Claim 25 wherein R^{16} is H.
27. A compound according to Claim 25 wherein R^{16} is methyl, ethyl or benzyl.
28. A compound according to Claim 26 wherein R^{15} is $-OR^{16}$.
29. A compound according to Claim 26 wherein R^{15} is $-NHR^{16}$.
30. A compound according to Claim 27 wherein R^{15} is $-OR^{16}$.
31. A compound according to Claim 27 wherein R^{15} is $-NHR^{16}$.

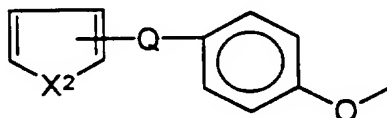
- 324 -

32. A compound according to Claim 23 wherein R^{15} is $-NHNH_2$.
33. A compound according to Claim 23 wherein n is 0 or 1 and R^3 and R^4 are independently H or methyl.
34. A compound according to Claim 32 wherein n is 0 or 1, and R^3 and R^4 are independently H or methyl.
35. A compound according to Claim 23 wherein Ar^1-Q-Ar^2-Y- is



wherein Q is $-O-$, $-CH_2-$, $-CF_2-$ or $-CH_2O-$, R^8 and R^{19} are independently H, lower alkyl, lower alkoxy, halogen, NH_2 or NO_2 .

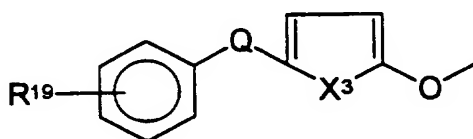
36. A compound according to Claim 23 wherein Ar^1-Q-Ar^2-Y- is



X^2 is $-S-$ or $-CH=N-$;

Q is $-CH_2-$, $-CF_2-$, $-O-$ or $-CH_2O-$.

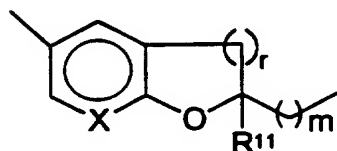
37. A compound according to Claim 23 wherein Ar^1-Q-Ar^2-Y- is



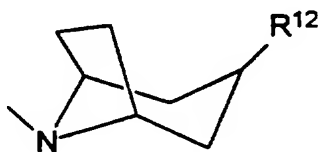
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- X^3 is -S-, -CH=N-;
 Q is -CH₂-, -CF₂-, -O- or -CH₂O-;
 R^{19} is H, lower alkyl, lower alkoxy, halogen,
 NH₂ or NO₂.

38. A compound according to Claim 23 wherein -Ar²-Y-R- is



39. A compound according to Claim 35 wherein
 Q is -CH₂- or -O-, and
 R^{19} is hydrogen or fluorine.
40. A compound according to Claim 36 wherein Q is -CH₂- or -O-, and R^{19} is hydrogen or fluorine.
41. A compound according to Claim 37 wherein Q is -CH₂- or -O-, and R^{19} is hydrogen or fluorine.
42. A compound according to Claim 41 wherein
 X^3 is -CH=N-.
43. A compound according to Claim 40 wherein
 X^2 is -S-.
44. A compound according to Claim 1 wherein Z is



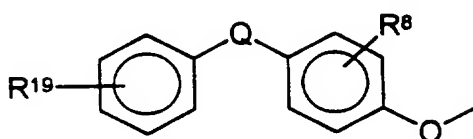
45. A compound according to Claim 44 wherein R^{12} is
 -(CH₂)₄COR¹⁵.

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46. A compound according to Claim 45 wherein R^{15} is $-OR^{16}$.

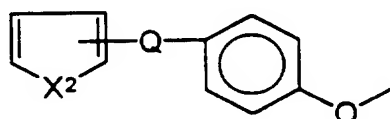
47. A compound according to Claim 45 wherein R^{15} is $-NHR^{16}$.

48. A compound according to Claim 45 wherein Ar^1-Q-Ar^2-Y- is



wherein Q is $-O-$, $-CH_2-$, $-CF_2-$ or $-CH_2O-$, R^8 and R^{19} are independently H , lower alkyl, lower alkoxy, halogen, NH_2 or NO_2 .

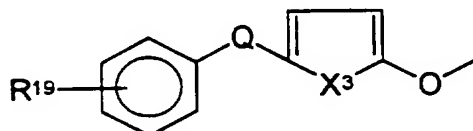
49. A compound according to Claim 45 wherein Ar^1-Q-Ar^2-Y- is



X^2 is $-S-$ or $-CH=N-$;

Q is $-CH_2-$, $-CF_2-$, $-O-$ or $-CH_2O-$.

50. A compound according to Claim 45 wherein Ar^1-Q-Ar^2-Y- is



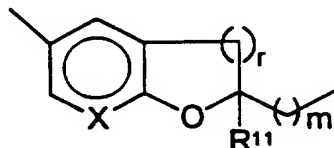
X^3 is $-S-$, $-CH=N-$;

Q is $-CH_2-$, $-CF_2-$, $-O-$ or $-CH_2O-$;

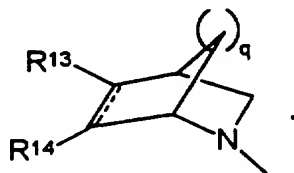
- 327 -

R^{19} is H, lower alkyl, lower alkoxy, halogen,
 NH_2 or NO_2 .

51. A compound according to Claim 45 wherein $-Ar^2-Y-R-$ is



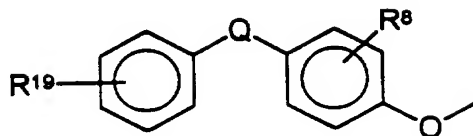
52. A compound according to Claim 48 wherein
 Q is $-CH_2-$ or $-O-$, and
 R^{19} is hydrogen or fluorine.
53. A compound according to Claim 49 wherein Q is $-CH_2-$ or $-O-$, and R^{19} is hydrogen or fluorine.
54. A compound according to Claim 50 wherein Q is $-CH_2-$ or $-O-$, and R^{19} is hydrogen or fluorine.
55. A compound according to Claim 54 wherein
 X^3 is $-CH=N-$.
56. A compound according to Claim 53 wherein
 X^2 is $-S-$.
57. A compound according to Claim 1 wherein Z is



58. A compound according to Claim 57 where R^{13} and R^{14} are each hydrogen.

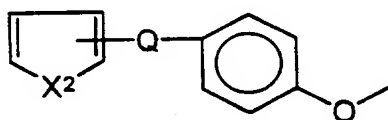
- 328 -

59. A compound according to Claim 57 wherein
 $\text{Ar}^1\text{-Q-Ar}^2\text{-Y-}$ is



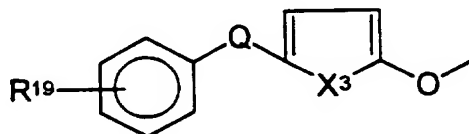
wherein Q is -O-, -CH₂-, -CF₂- or -CH₂O-, R⁸ and R¹⁹ are independently H, lower alkyl, lower alkoxy, halogen, NH₂ or NO₂.

60. A compound according to Claim 57 wherein
 $\text{Ar}^1\text{-Q-Ar}^2\text{-Y-}$ is



X² is -S- or -CH=N-;
 Q is -CH₂-, -CF₂-, -O- or -CH₂O-.

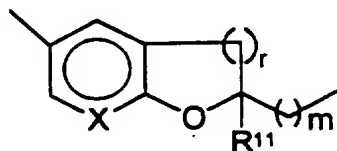
61. A compound according to Claim 57 wherein
 $\text{Ar}^1\text{-Q-Ar}^2\text{-Y-}$ is



X³ is -S-, -CH=N-;
 Q is -CH₂-, -CF₂-, -O- or -CH₂O-;
 R¹⁹ is H, lower alkyl, lower alkoxy, halogen, NH₂ or NO₂.

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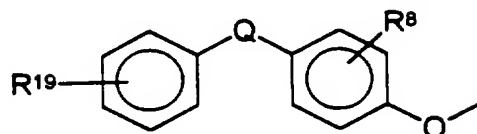
62. A compound according to Claim 57 wherein $-\text{Ar}^2-\text{Y}-\text{R}-$ is



63. A compound according to Claim 59 wherein
 Q is $-\text{CH}_2-$ or $-\text{O}-$, and
 R^{19} is hydrogen or fluorine.
64. A compound according to Claim 60 wherein Q is $-\text{CH}_2-$ or $-\text{O}-$, and R^{19} is hydrogen or fluorine.
65. A compound according to Claim 61 wherein Q is $-\text{CH}_2-$ or $-\text{O}-$, and R^{19} is hydrogen or fluorine.
66. A compound according to Claim 65 wherein
 X^3 is $-\text{CH}=\text{N}-$.
67. A compound according to Claim 64 wherein
 X^2 is $-\text{S}-$.
68. A compound according to Claim 1 wherein Z is a monocyclic or bicyclic heteroaromatic moiety having at least one heteroatom, wherein the heteroatom is nitrogen, and wherein the monocyclic heteroaromatic moiety comprises a 5- or 6-membered ring and the bicyclic heteroaromatic moiety comprises a fused 9- or 10-membered ring.
69. A compound according to Claim 68 wherein Z is selected from the group consisting of imidazolyl, benzimidazolyl, imidazopyridinyl, triazopyridinyl, purinyl, triazolyl, and thiazolyl.

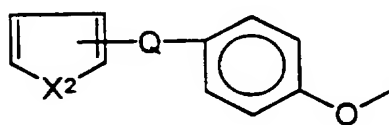
- 330 -

70. A compound according to Claim 69 wherein
 $\text{Ar}^1\text{-Q-Ar}^2\text{-Y-}$ is



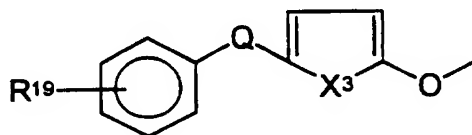
wherein Q is -O-, -CH₂-, -CF₂- or -CH₂O-, R⁸ and R¹⁹ are independently H, lower alkyl, lower alkoxy, halogen, NH₂ or NO₂.

71. A compound according to Claim 69 wherein
 $\text{Ar}^1\text{-Q-Ar}^2\text{-Y-}$ is



X² is -S- or -CH=N-;
 Q is -CH₂-, -CF₂-, -O- or -CH₂O-.

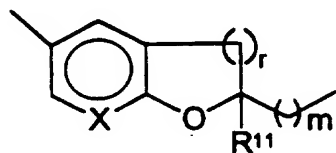
72. A compound according to Claim 69 wherein
 $\text{Ar}^1\text{-Q-Ar}^2\text{-Y-}$ is



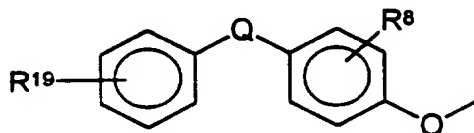
X³ is -S-, -CH=N-;
 Q is -CH₂-, -CF₂-, -O- or -CH₂O-;
 R¹⁹ is H, lower alkyl, lower alkoxy, halogen, NH₂ or NO₂.

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73. A compound according to Claim 69 wherein $-\text{Ar}^2-\text{Y}-\text{R}-$ is



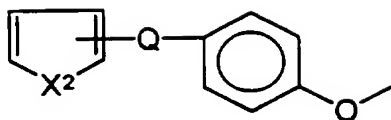
74. A compound according to Claim 70 wherein
 Q is $-\text{CH}_2-$ or $-\text{O}-$, and
 R^{19} is hydrogen or fluorine.
75. A compound according to Claim 71 wherein Q is $-\text{CH}_2-$ or $-\text{O}-$, and R^{19} is hydrogen or fluorine.
76. A compound according to Claim 72 wherein Q is $-\text{CH}_2-$ or $-\text{O}-$, and R^{19} is hydrogen or fluorine.
77. A compound according to Claim 76 wherein
 X^3 is $-\text{CH}=\text{N}-$.
78. A compound according to Claim 75 wherein
 X^2 is $-\text{S}-$.
79. A compound according to Claim 1 wherein
 $\text{Ar}^1-\text{Q}-\text{Ar}^2-\text{Y}-$ is



wherein Q is $-\text{O}-$, $-\text{CH}_2-$, $-\text{CF}_2-$ or $-\text{CH}_2\text{O}-$, R^8 and R^{19} are independently H, lower alkyl, lower alkoxy, halogen, NH_2 or NO_2 .

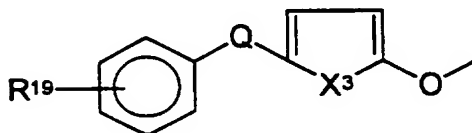
80. A compound according to Claim 1 wherein $\text{Ar}^1-\text{Q}-\text{Ar}^2-\text{Y}-$ is

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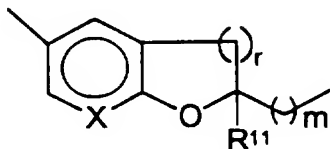
X^2 is -S-
 or -CH=N-;
 Q is -CH₂-, -CF₂-, -O- or -CH₂O-.

81. A compound according to Claim 1 wherein
 Ar^1-Q-Ar^2-Y- is



X^3 is -S-, -CH=N-;
 Q is -CH₂-, -CF₂-, -O- or -CH₂O-;
 R^{19} is H, lower alkyl, lower alkoxy, halogen,
 NH₂ or NO₂.

82. A compound according to Claim 1 wherein $-Ar^2-Y-R-$
 is



83. A compound according to Claim 79 wherein
 Q is -CH₂- or -O-, and
 R^{19} is hydrogen or fluorine.
84. A compound according to Claim 80 wherein Q is -CH₂-
 or -O-, and R^{19} is hydrogen or fluorine.
85. A compound according to Claim 81 wherein Q is -CH₂-
 or -O-, and R^{19} is hydrogen or fluorine.
86. A compound according to Claim 85 wherein

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X³ is -CH=N-.

87. A compound according to Claim 84 wherein
X² is -S-.

88. A compound according to Claim 1 which is selected
from the group consisting of:

N-[1-[2-[4-(phenylmethyl)phenoxy]ethyl]-
piperidin-4-yl]acetamide;

N-[1-[2-[4-(phenylmethyl)phenoxy]ethyl]-
pyrrolidin-3-yl]urea;

N-[1-[2-[4-(phenylmethyl)phenoxy]ethyl]-
piperidin-4-yl]urea; and

5-[2-methyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-
piperidin-4-yl]-1H-tetrazole, monohydrate.

89. A compound according to Claim 8 which is selected
from the group consisting of:

3-[[3-[4-(phenylmethyl)phenoxy]propyl]amino]-
propanoic acid;

3-[methyl[3-[4-(phenylmethyl)phenoxy]propyl]-
amino]propanoic acid;

3-[[4-[4-(phenylmethyl)phenoxy]butyl]amino]-
propanoic acid;

3-[[3-(4-phenoxyphenoxy)propyl]amino]-
propanoic acid;

3-[methyl[3-(4-phenoxyphenoxy)propyl]amino]-
propanoic acid;

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3-[[4-(4-phenoxyphenoxy)butyl]amino]-
propanoic acid;

3-[[3-[4-[(4-fluorophenyl)methyl]phenoxy]propyl]-
methylamino]propanoic acid, monohydrochloride;

3-[methyl[3-[4-(2-thienylmethyl)phenoxy]propyl]amino]-
propanoic acid, monohydrochloride; and

3-[methyl[3-[4-(3-thienylmethyl)phenoxy]propyl]amino]-
propanoic acid, monohydrochloride.

90. A compound according to Claim 10 which is selected
from the group consisting of:

ethyl 3-[[3-[4-(phenylmethyl)phenoxy]propyl]-
amino]propanoate;

phenylmethyl 3 [methyl[3-[4-(phenylmethyl)-
phenoxy]propyl]amino]propanoate;

ethyl 3-[[3-(4-phenoxyphenoxy)propyl]-
amino]propanoate;

ethyl 3-[methyl-[3-[4-(phenylmethyl)phenoxy]-
propyl]amino]propanoate;

methyl 3-[methyl[3-[4-(phenylmethyl)phenoxy]-
propyl]amino]propanoate, hydrate;

ethyl 3-[4-[4-(phenylmethyl)phenoxy]-
butyl]amino]propanoate;

phenylmethyl 3-[[4-[4-(phenylmethyl)phenoxy]-
butyl]amino]propanoate;

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phenylmethyl 3-[[3-(4-phenoxyphenoxy)-
propyl]amino]propanoate;

phenylmethyl 3-[methyl[3-(4-phenoxyphenoxy)-
propyl]amino]propanoate;

phenylmethyl 3-[[4-(4-phenoxyphenoxy)-
butyl]amino]propanoate;

methyl 3-[methyl[3-[4-(2-thienylmethyl)-
phenoxy]propyl]amino]propanoate;

methyl 3-[3-[4-[(4-fluorophenyl)methyl]-
phenoxy]propyl]-methylanino]propanoate;

ethyl 3-[[4-[4-phenoxyphenoxy]butyl]-
amino]propanoate;

methyl 3-[methyl[3-[4-(3-thienylmethyl)-
phenoxy]propyl]amino]propanoate; and

methyl 3-[[3-[4-(4-fluorophenoxy)phenoxy]-
propyl]methylanino]propanoate.

91. A compound according to Claim 28 which is selected
from the group consisting of:

1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidine-
carboxylic acid, monohydrochloride, hydrate;

1-[2-(4-phenoxyphenoxy)ethyl]piperidine-4-
carboxylic acid, monohydrochloride;

1-[2-[4-[(4-fluorophenyl)methyl]phenoxy]ethyl]-
piperidine-4-carboxylic acid, monohydrochloride;

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1-[2-[4-(3-thienylmethyl)phenoxy]ethyl]piperidine-4-carboxylic acid, monohydrochloride;

1-[2-[4-(4-fluorophenoxy)phenoxy]ethyl]piperidine-4-carboxylic acid, monohydrochloride;

1-[2-[4-[(3-fluorophenyl)methyl]phenoxy]ethyl]-4-carboxylic acid, monohydrochloride; and

1-[2-[4-(2-thienylmethyl)phenoxy]ethyl]piperidine-4-carboxylic acid, monohydrochloride.

92. A compound according to Claim 29 which is selected from the group consisting of:

1-[2-[4-(phenylmethyl)phenoxy]ethyl]piperidine-4-carboxamide;

1-[2-[4-(phenylmethyl)phenoxy]ethyl]-3-piperidinecarboxamide;

(+)-2S- α -methyl-1-[2-[4-(phenylmethyl)-phenoxy]ethyl]-4- α -pyridinecarboxamide; and

(cis)-2R,6-dimethyl-1-[2-[4-(phenylmethyl)phenoxy]-ethyl]piperidine-4-carboxamide.

93. A compound according to Claim 30 which is selected from the group consisting of:

ethyl 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-3-piperidine carboxylate;

ethyl 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidine-carboxylate, monohydrochloride;

1-[2-(4-phenoxyphenoxy)ethyl]-4-

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piperidinecarboxamide;

methyl 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-
3-pyrrolidineacetate;

methyl 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-
3-pyrrolidine-carboxylate;

ethyl 1-[2-(4-phenoxyphenoxy)ethyl]-4-
piperidinecarboxylate, monohydrochloride;

(±)ethyl 2-methyl-1-[2-[4-(phenylmethyl)phenoxy]-
ethyl]piperidine-4-carboxylate;

ethyl 1-[2-(4-phenoxyphenoxy)ethyl]piperidine-4-
acetate, monohydrochloride;

ethyl 1-[2-[[5-(phenylmethyl)thien-2-yl]oxy]ethyl]-
piperidine-4-carboxylate;

ethyl 1-[2-[4-[[3-fluorophenyl)methyl]phenoxy]ethyl]-
piperidine-4-carboxylate;

ethyl 1-[2-[4-(2-thienylmethyl)phenoxy]ethyl]-
piperidine-4-carboxylate;

ethyl 1-[2-[4-[(4-fluorophenyl)methyl]phenoxy]ethyl]-
piperidine-4-carboxylate;

ethyl 1-[2-[4-(3-thienylmethyl)phenoxy]ethyl]-
piperidine-4-carboxylate;

ethyl 1-[2-[4-(4-fluorophenoxy)phenoxy]ethyl]-
piperidine-4-carboxylate, monohydrochloride; and

methyl(cis)-2R,6-dimethyl-1-[2-[4-(phenylmethyl)-
phenoxy]ethyl]piperidine-4-carboxylate.

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94. A compound according to Claim 46 which is

methyl 8-[2-[4-(phenylmethyl)phenoxy]ethyl]-8-
azabicyclo[3.2.1]octane-3-carboxylate.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/12365

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D295/08 A61K31/13 A61K31/395 C07D277/24 C07D213/69
C07D213/74 C07D295/12 C07D277/34 C07D213/64 C07D213/30
C07D333/16 C07D307/42 C07C217/16 C07C229/12 C07C229/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 35, no. 17, 1992 WASHINGTON US, pages 3156-3169, R. LABAUDINIÈRE, ET AL. 'omega-((omega-arylalkyl)aryl)alkanoic acids: a new class of specific LTA4 hydrolase inhibitors' * page 3160-1: table I and II *	1
A	WO,A,94 00420 (THE SCRIPPS RESEARCH INSTITUTE) 6 January 1994 see claims 1,21 -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

21 December 1995

Date of mailing of the international search report

15. 01. 96

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Van Bijlen, H

INTERNATIONAL SEARCH REPORT

In: tional application No.

PCT/US 95/ 12365

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please see attached sheet ./.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Institution on patent family members

PCT/LJ 95/12365

03-10-95
24-01-94



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5/02, 5/04, 5/05

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(30) Priority Data:

08/339,958

15 November 1994 (15.11.94)

US

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(72) Inventor: HOYE, Thomas, R.; 154 Montrose Place, St. Paul, MN 55104 (US).

(74) Agent: VIKSNINS, Ann, S.; Schwegman, Lundberg & Woessner, P.O. Box 2938, Minneapolis, MN 55402 (US).

(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG).

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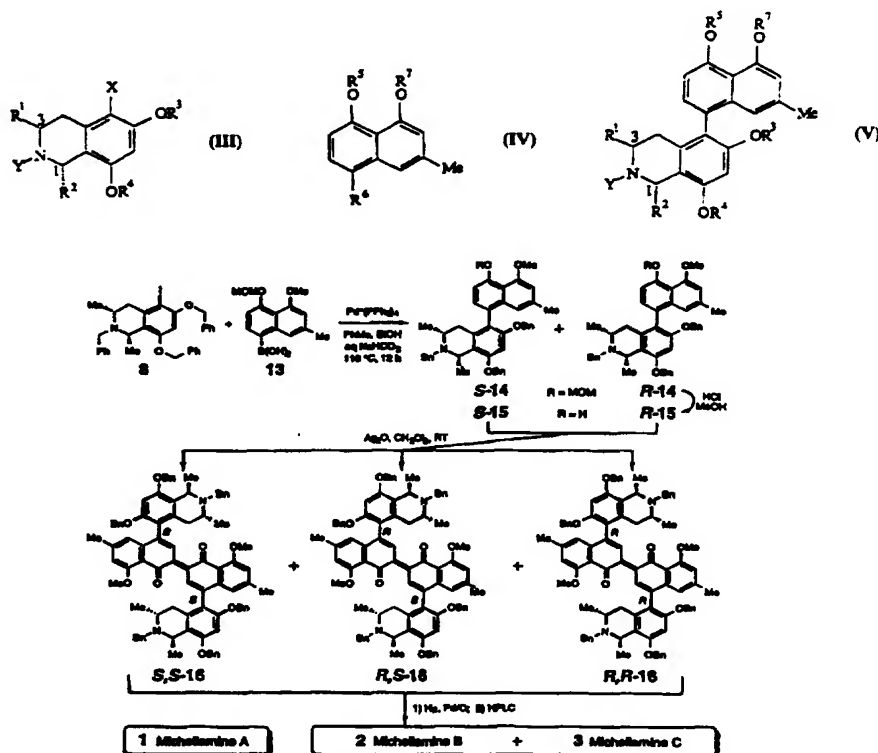
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHOD AND INTERMEDIATES FOR THE SYNTHESIS OF KORUPENSAMINES

(57) Abstract

A method of preparing a korupensamine or an analog thereof comprising: (a) reacting a compound of formula (III), wherein each of R¹ and R² is CH₃ or H, X is I, Y is (C₁-C₄)alkyl, benzyl or CHO, and each of R³ and R⁴ is (C₁-C₄)alkyl, benzyl, (C₂-C₅)acyl or an acid-labile hydroxy protecting group; with a compound of formula (IV), wherein R⁵ is benzyl, (C₂-C₅)acyl or an acid-labile hydroxy protecting group, R⁶ is B(OH)₂, and R⁷ is (C₁-C₄)alkyl; in the presence of a Pd(0) catalyst and an inorganic base in an organic solvent, to yield a compound of formula (V), wherein Y, R¹, R², R³, R⁴, R⁵ and R⁷ are as defined above for compounds of formula (III) and (IV). Additionally the intermediates of formula (III), wherein X is Br, Cl or I, Y is H, (C₁-C₄)alkyl, benzyl, or CHO, each of R¹ and R² is H or CH₃, R³ is a protecting group selected from the group consisting of (C₁-C₄)alkyl, benzyl, (C₂-C₅)acyl and an acid-labile hydroxy protecting group; and R⁴ is H or (C₂-C₅)acyl; or wherein X is Br, Cl or I, Y is H, (C₁-C₄)alkyl, benzyl, or CHO, each of R¹ and R² is H or CH₃, R³ is H or (C₂-C₅)acyl and R⁴ is a protecting group selected from the group consisting of (C₁-C₄)alkyl, benzyl, (C₂-C₅)acyl and an acid-labile hydroxy protecting group; and the intermediates of formula (IV), wherein R⁶ is Cl, Br, I, B(OH)₂, an anhydride or ester of B(OH)₂, or OSO₂R⁹, wherein R⁹ is (C₁-C₄)perfluoroalkyl, and each of R⁵ and R⁷ is H, (C₁-C₄)alkyl, benzyl, (C₂-C₅)acyl or an acid-labile hydroxy protecting group.



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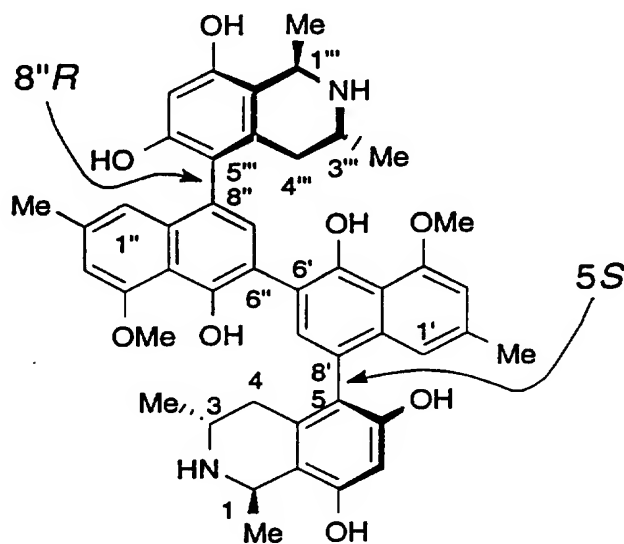
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METHOD AND INTERMEDIATES FOR THE
SYNTHESIS OF KORUPENSAMINES

Background of the Invention

5

Michellamines A (1), B (2), and C (3) constitute a family of anti-HIV, atropisomeric, naphthylisoquinoline alkaloids. All are fully protective against both HIV-1 and HIV-2 infected CEM-SS cells with EC₅₀ values of 2-13 μM. Michellamine B, the most studied and most prevalent of the group, completely protects MT-2 cells from both AZT-resistant and pyridone-resistant strains of HIV-1. The structure of michellamine B is shown below:



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Michellamine B (2)

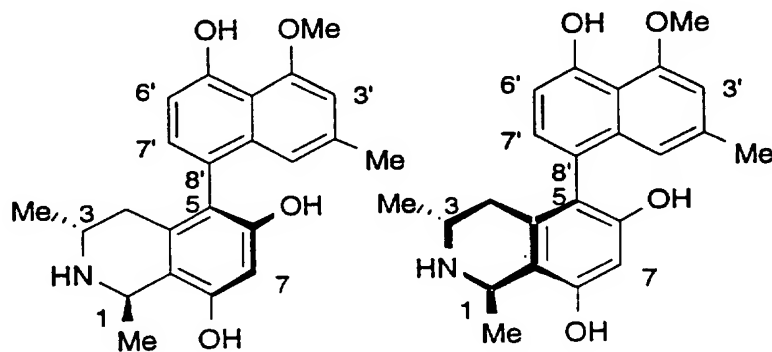
Michellamine B possesses a multilevel mode of action including an inhibition of the viral reverse transcriptase as well as blockage of cellular fusion and syncytium formation. In light of these promising properties, as well as favorable initial toxicity evaluation, michellamine B has been selected by the National Cancer Institute for IND-directed preclinical development. See, for example, K.P. Manfredi et al., *J.*

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Med. Chem., **34**, 3402 (1991) and M.R. Boyd et al., J. Med. Chem., **37**, 1740 (1994).

The michellamines were isolated from a previously unidentified plant, *Ancistrocladus korupensis*--a liana found only in the rain forest of a limited region in Cameroon. Supply continuity and sufficiency are important concerns for further drug development. Atropisomers **1-3** are unique among known naphthylisoquinoline alkaloids in their dimeric nature, in the locus of the naphthalene to isoquinoline biaryl bond, and in the extent of free hydroxyl group adornment. The relative configurations of the stereogenic biaryl axes in each of **1-3** were established by identification of NOE interactions between the peri-H(1') and -H(1'') and one or the other of the diastereotopic protons at C(4) and C(4''). The absolute configurations at C(1)/C(1'') and C(3)/C(3'') were assigned by degradation to *R*-alanine and *R*-3-aminobutyric acid, respectively. See, M.R. Boyd et al., as cited above, G. Bringmann et al., Angew. Chem. Int. Ed. Eng., **32**, 1190 (1993) and G. Bringmann et al., Tetrahedron, **32**, 9643 (1994). The configurations at 5/8' and 8''/5''' of michellamines A, B and C are *S/S*, *S/R* and *R/R*, respectively.

Two syntheses of michellamine A were recently described by G. Bringmann et al., Tetrahedron, **32**, 9643 (1994), and T.R. Kelly et al., Tetrahedron Lett., **35**, 7621 (1994). An acyl derivative of a sample of the natural product korupensamine A (**4**), which co-exists with the michellamines in the plant, was oxidatively dimerized with silver oxide to yield a binaphthylidendione, which was reduced and deacylated to yield michellamine A. The structure of korupensamine A (**4**) and its atropisomer ("korupensamine C" (**4'**)) are shown below:

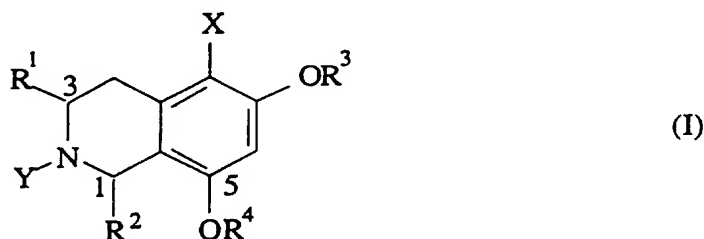
Korupensamine A (**4**)Korupensamine C (**4'**)

Compound 4' has been referred to as korupensamine B by G. Bringmann et al., *J. Org. Chem.*, **59**, 6349 (1994). In view of the ability to synthesize michellamines from these compounds in no more than five steps, a need exists for synthetic methods and intermediates which can be employed to prepare korupensamines.

Summary of the Invention

The present invention provides intermediates useful for the synthesis of korupensamines and thus for the synthesis of michellamines and their analogs.

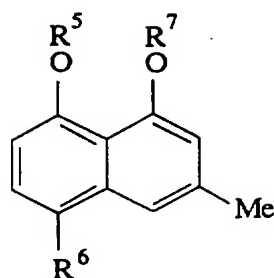
For example, the present invention provides a compound of the general formula (I):



wherein X is Br, Cl or I; Y is H, (C₁-C₄)alkyl, benzyl, or CHO; each of R¹ and R² is H or CH₃ and each of R³ and R⁴ is H, (C₁-C₄)alkyl, benzyl, (C₂-C₅)acyl, or an acid-labile hydroxy protecting group such as (C₁-C₄)alkoxy(C₁-C₄)alkyl, tetrahydropyranyl, or (R⁸)₃Si, wherein each R⁸ is (C₁-C₄)alkyl. Preferably, X is I, R¹ and R² are CH₃, and R³, R⁴ and Y are the same protecting group, i.e., R³=R⁴=Y=benzyl.

As shown in compound 2, a broken line indicates a bond that extends below the plane of the ring, i.e., below the plane of the page, and a wedged line indicates a bond that extends above the plane of the page. Thus, to prepare korupensamines A and C, the 1*R*,3*R*-isomer of (I) is employed. However, the procedures disclosed by G. Bringmann et al., cited above, permit the preparation of all the 1,3-isomers of formula (I), wherein X=H; hence all the 1,3-isomers of formula (I) are considered to be within the scope of the invention.

The present invention also provides compounds of the formula (II):



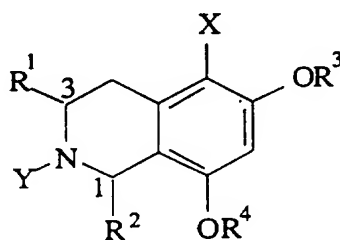
(II)

wherein R^6 is Cl, Br, I, $B(OH)_2$, an anhydride or ester of $B(OH)_2$, or OSO_2R^9 ,
 wherein R^9 is (C_1-C_4) perfluoroalkyl, and each of R^5 and R^7 is H, (C_1-C_4) alkyl,
 5 benzyl, (C_2-C_5) acyl or an acid-labile hydroxy protecting group, as described above.
 Preferably, R^6 is Br or $B(OH)_2$, R^5 is an acid-labile protecting group, and R^7 is H or CH_3 .

The compound of formula II wherein R^6 is $B(OH)_2$ can be prepared
 from a compound of formula II wherein R^6 is halo, by lithiation and reaction of the
 10 lithiated compound with $B(OMe)_3$, following protection of the two OH groups, i.e.,
 wherein R^5 and R^7 are not H or acyl. The compound of formula II wherein R^6 is
 $B(OH)_2$ and R^5 and R^7 are not H or acyl can be coupled via Pd(0) catalyzed coupling
 with a compound of formula I, wherein X is I, $R^1=R^2=CH_3$, and R^3 , R^4 and Y are
 not H, to yield N- and 6,8,4',5' hydroxyl-protected korupensamines. Selective
 15 removal of the 5' hydroxyl protecting group, followed by oxidative 6'/6' coupling,
 reduction and, if necessary, removal of the remaining R^3 , R^4 and Y protecting
 groups, wherein R^7 is CH_3 , affords a mixture of michellamines A-C, which can be
 separated by chromatographic techniques.

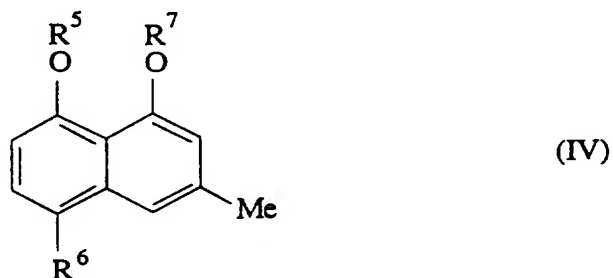
Thus, a further aspect of the present invention is a method to prepare a
 20 korupensamine, preferably korupensamine A or B, or an analog thereof comprising:

(a) reacting a compound of the formula (III):

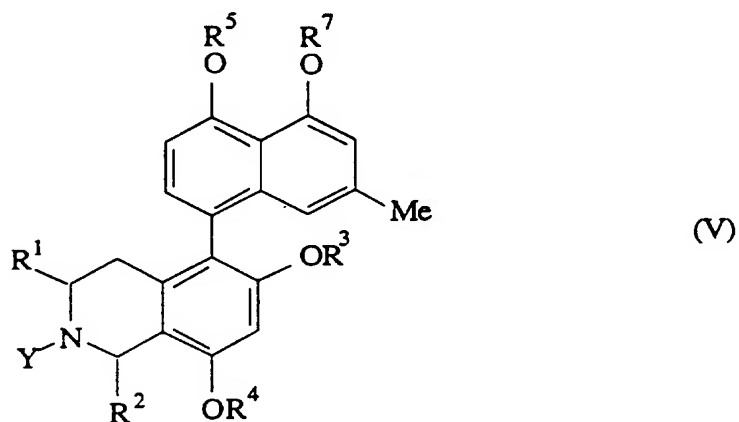


(III)

wherein each of R^1 and R^2 is CH_3 or H , X is I , Y is (C_1-C_4) alkyl, benzyl or CHO , and each of R^3 and R^4 is (C_1-C_4) alkyl, benzyl, (C_2-C_5) acyl or an acid-labile hydroxy protecting group; with a compound of the formula (IV):



wherein R^5 is benzyl, (C_2-C_5) acyl or an acid-labile hydroxy protecting group, R^6 is $B(OH)_2$, and R^7 is (C_1-C_4) alkyl; in the presence of a $Pd(0)$ catalyst and an inorganic base in an organic solvent, to yield a compound of the formula (V):



wherein Y , R^1 , R^2 , R^3 , R^4 , R^5 and R^7 are as defined above; and

(b) removing protecting groups R^3 , R^4 , R^5 and Y to yield a compound of formula V wherein R^1 and R^2 are each H or CH_3 , R^7 is (C_1-C_4) alkyl, and Y , R^2 , R^3 , R^4 , and R^5 are H . Preferably, R^1 , R^2 and R^7 are CH_3 , R^5 is an acid-labile protecting group, preferably methoxymethyl, that is subsequently removed by exposing V to dilute aqueous acid, and Y , R^3 and R^4 are benzyl that are subsequently removed by hydrogenolysis. Most preferably, the 1*R*,3*R*-isomer of III is employed, which yields a mixture of korupensamines A and C.

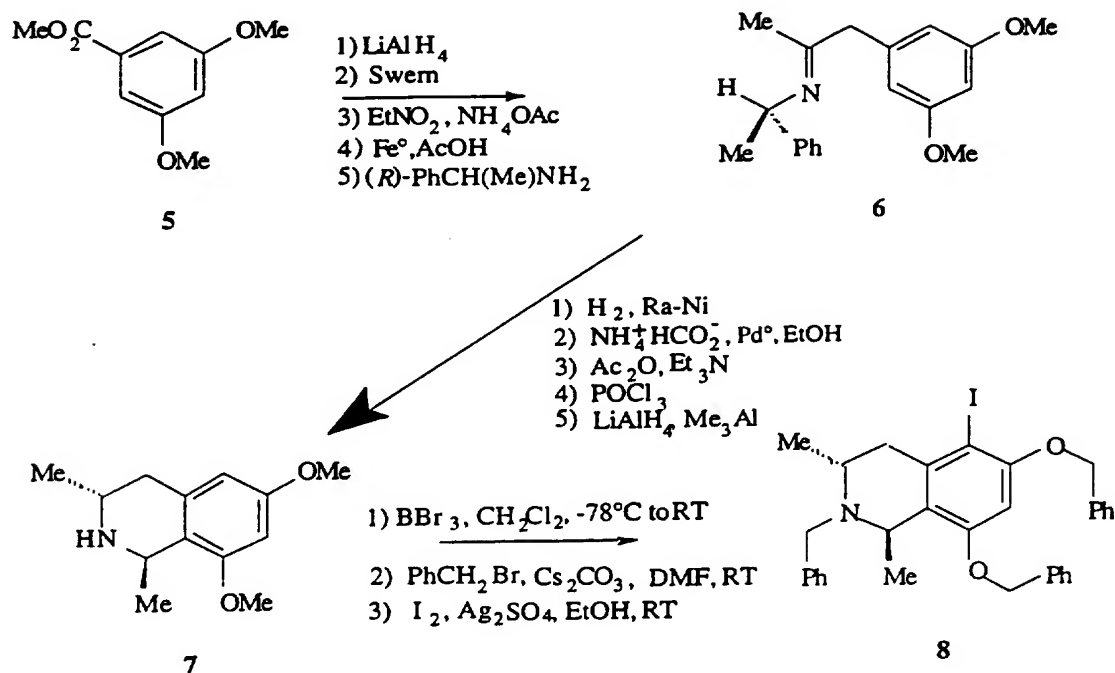
Brief Description of the Figures

Figure 1 is a reaction scheme summarizing the reaction of compounds 8 and 13 to yield korupensamine derivatives *S*-14 and *R*-14, and the conversion of these compounds to michellamines A-C.

Detailed Description of the Invention

As shown in Scheme I, following the general route developed by G. Bringmann et al., Angew. Chem. Int. Ed. Eng., **25**, 913 (1986) and G. Bringmann, et al., Liebigs Ann. Chem., 877 (1993), the non-racemic tetrahydroisoquinoline 7 (I, Y=H, R¹=R²=R³=R⁴=CH₃), was prepared from methyl 3,5-dimethoxybenzoate (5) via Raney nickel reduction of the non-racemic α -methylbenzylimine 6, following the methodology of D.E. Nichols et al., J. Med. Chem., **16**, 480 (1973). Demethylation of 7 with excess boron tribromide gave a diphenol amine•HBr salt, which was tribenzylated with benzyl bromide and cesium carbonate in DMF at room temperature (85%, two steps). Regiospecific iodination with iodine and silver sulfate gave C(5)-activated, benzyl protected 8 (66%), in accord with the methodology of W.W. Wy, Tetrahedron Lett., **34**, 6223 (1993). Likewise, direct bromination with Br₂ yields the corresponding brominated compound.

Scheme I.



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Generally, demethylation of 7 yields a compound of formula I wherein Y, R^3 and R^4 are H, and the hydroxyl groups can be reacted with other protecting groups, such as those disclosed hereinabove. Likewise, the iodo moiety can be replaced by Br or Cl by a variety of halogen exchange reactions, such as by lithiation, following reaction with elemental halogen. Replacement of $(R)\text{-PhCH(Me)NH}_2$ with PhCH_2NH_2 and/or reaction with the corresponding 3,5-dimethoxyphenylacetaldehyde yields compounds of formula I wherein R^1 and/or R^2 is H. Synthesis of all the possible 1,3-isomers of 7, as well as compounds of formula 7 wherein one OMe group has been replaced by OH, is disclosed by G. Bringmann, et al., *Liebigs Ann. Chem.*, 877 (1993).

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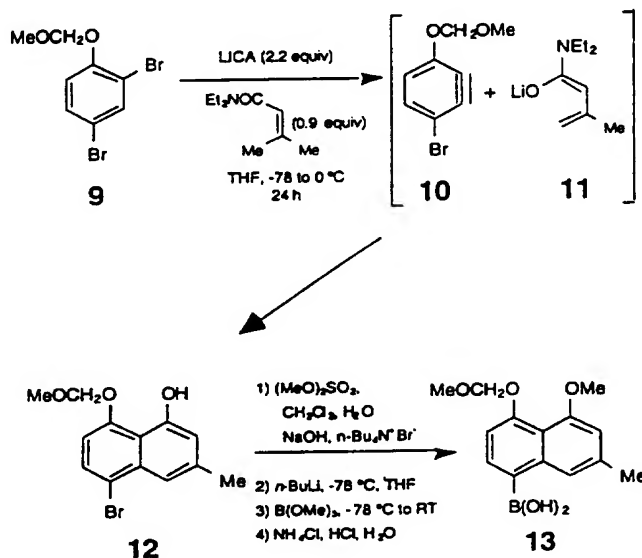
As shown in Scheme II, boronic acid 13 (II, $\text{R}^5=\text{CH}_2\text{OCH}_3$, $\text{R}^7=\text{CH}_3$, $\text{R}^6=\text{B(OH)}_2$) was efficiently prepared from methoxymethyl (MOM)-protected 2,4-dibromophenol (9) by a regioselective benzyne annulation reaction. Treatment of 9 with an excess of lithium cyclohexylisopropylamide and N,N-diethyl seneciarnide, as disclosed by M. Watanabe et al., *Chem. Pharm. Bull.*, 34, 2810 (1986), gave 12 (II, $\text{R}^5=\text{CH}_2\text{OCH}_3$, $\text{R}^7=\text{CH}_3$, $\text{R}^6=\text{Br}$) presumably by way of

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benzyne **10** and lithium enolate **11**. Although the yield of this reaction was only 29%, the transformation was very reproducible. O-Methylation with methylsulfate, lithiation, and boronic acid synthesis with $B(OCH_3)_3$ followed standard protocols to yield **13**.

5 Reaction of a protected compound of formula II wherein $R^6=Li$ with Cl_2 or I_2 yields II, $R^6=Cl$ or I . Likewise, other acid-labile protecting groups can be used in place of $MeOCH_2$ in compound **9**, and $R^7=CH_3$ in formula II can readily be replaced with other protecting groups.

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Scheme II.

As shown in Figure 1, the palladium(0) catalyzed cross-coupling of **8** with **13** provided an about 4:3 ratio of the hindered atropisomers *S*-**14** and *R*-**14** (40-80%). Palladium(0) catalyzed cross-coupling is typically carried out in the presence of a base and an organic solvent. A preferred embodiment of the invention utilizes tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) as the source of palladium(0) catalyst, saturated sodium bicarbonate ($NaHCO_3$) as the base and toluene as the organic solvent. Other useful sources of $Pd(0)$ catalysts include those disclosed in Larock et al. (U.S. Patent No. 5,233,059, Col. 6) and Blaser et al. (U.S. Patent No. 4,335,054, Col. 6 and Col. 7), which may alternatively be used in the method of present invention under conditions wherein $Pd(0)$ is generated. Bases useful in the present invention are those which are adequately soluble in the reaction medium. Although an inorganic base is preferred, an organic base can also be used.

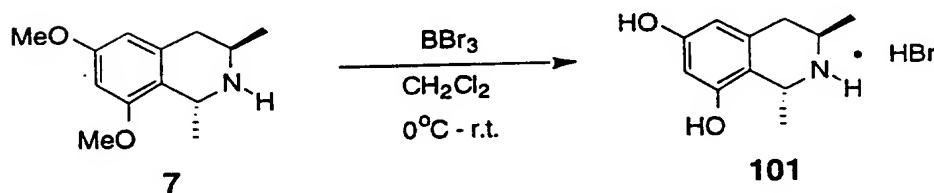
Representative bases are disclosed at Col. 7 of the Larock et al. patent, and Col. 7 of the Blaser et al. patent, as cited above. Examples of suitable organic solvents include, in addition to the preferred toluene, tetrahydrofuran, ethers, glycol ethers, dimethylsulfoxide, dimethyl formamide, acetonitrile, acetamide, dimethylacetamide, and hexamethylphosphoramide.

Hydrolysis of the methoxymethyl (MOM) ethers of **14** gave the naphthols **15** (75-100%), which could be separated by careful normal-phase HPLC. Hydrogenolysis of the benzyl groups in a mixture of the naphthols **15** provided an about 4:3 mixture of korupensamine A and "C" atropisomers **4** and **4'**.

The mixture of tribenzylated naphthols **15** underwent remarkably efficient oxidative coupling with excess silver oxide in methylene chloride (or CDCl₃) at room temperature by the methodology of H. Laatsch, Liebigs Ann. Chem., 1321, (1980), to give the purple indigoids *R,S*-**16**, *S,S*-**16**, and *R,R*-**16** in an about 2:1:1 ratio (about 100%). The cross-ring quinones **16** could be reduced to the corresponding colorless binaphthols (sodium dithionite, H₂O, CH₂Cl₂ or NaBH₄, CH₂Cl₂, EtOH) and then perdebenzylated. More conveniently, direct exposure of **16** to one atmosphere of hydrogen in methylene chloride/methanol over 10% Pd/C resulted in simultaneous reductive bleaching of the indigoid and complete hydrogenolysis of the six benzyl groups. Michellamines A-C were cleanly (as judged from the crude ¹H NMR spectrum) produced with nearly quantitative mass recovery. Separation of a small portion on amino-bonded phase [7:1 CH₂Cl₂:0.1 weight % (NH₄)₂CO₃ in methanol] has thus far provided a pure sample of michellamine A (**1**) along with an about 2:1 mixture of michellamines B (**2**) and C (**3**), as determined by NMR analysis.

The invention will further be described by reference to the following detailed examples.

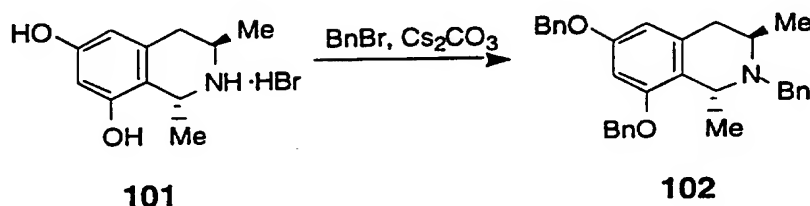
Example 1. Preparation of 1(R), 3(R)-1,2,3,4-tetrahydro-6,8-dihydroxy-1,3-dimethylisoquinoline hydrobromide salt (101)



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(1R, 3R)-1,2,3,4-tetrahydro-6,8-dimethoxy-1,3-dimethylisoquinoline was prepared as described in G. Bringmann et al., Liebigs Ann. Chem., 877 (1993) and 50.7 mg (0.2 mmol) placed in an oven dried flask (5 mL r.b.) containing CH_2Cl_2 (1 mL) and a magnetic stir bar. The flask was sealed with a rubber septum and the atmosphere was exchanged for nitrogen. The reaction mixture was cooled to -78 °C and a BBr_3 solution (1 mL, 4.3 equiv, 1 M in CH_2Cl_2) was added via syringe. The reaction mixture was immediately allowed to warm to room temperature and stir. After 10 h, the flask was cooled to -78 °C and carefully quenched with 1.5 mL of MeOH. The stir bar was removed and the reaction mixture was concentrated in vacuo to yield a brown oil. MeOH (3.5 mL) was added to dissolve the oil and the reaction mixture was concentrated again. This quenching procedure was repeated 6-8 times until the hydrobromide salt **101** (62.8 mg, 100%) was isolated as brown crystals; ^1H NMR (500 MHz, CD_3OD): δ 6.23 [d, J = 1.8 Hz, Ar-H(7)], 6.12 [d, J = 2.1 Hz, Ar-H(5)], 4.64 [q, J = 6.7 Hz, CHCH_3], 3.75 [ddq, J = 11.6, 4.6 and 6.5 Hz, CH_2CHCH_3], 2.98 [dd, J = 17.4 and 4.6 Hz, $\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_3$], 2.75 [dd, J = 17.4 and 11.6 Hz, $\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_3$], 1.59 [d, J = 7.0 Hz, CHCH_3], and 1.46 [d, J = 6.4 Hz, CH_2CHCH_3]; ^{13}C NMR (125 MHz, CD_3OD): δ 158.97, 156.10, 133.65, 112.61, 107.01, 101.94, 49.35, 45.35, 34.59, 19.23, and 18.33; m.p. (range): 140-143 °; Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_2\text{Br}$: C, 48.19; H, 5.88. Found: C, 48.35; H, 5.69.

**Example 2. Preparation of Tribenzylprotected Tetrahydroisoquinoline
(102)**

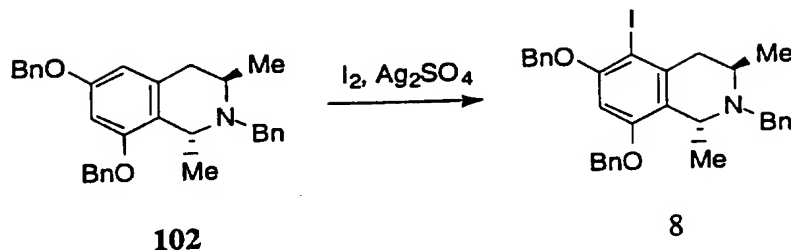


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To a stirred solution of 1(R), 3(R)-1,2,3,4-tetrahydro-6,8-dihydroxy-1,3-dimethyl-isoquinoline hydrobromide salt (0.39 g, 1.4 mmol) in 15 mL of dry DMF was added benzylbromide (1.70 g, 10.0 mmol), followed by the addition of cesium carbonate (2.40 g, 7.4 mmol). After being stirred for 6 h at room temperature, the reaction mixture was poured into H₂O (100 mL), and EtOAc (100 mL) was added. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc/Et₃N; 9:1:0.1) to yield tribenzyl-protected tetrahydroisoquinoline **102** (0.57 g, 86 %) as a thick yellow oil.; ¹H NMR (500 MHz, CDCl₃): δ 7.42-7.21 [m, benzyl ArH], 6.42 [d, J = 2.0 Hz, ArH(7)], 6.34 [d, J = 2.0 Hz, ArH(5)], 4.99 [s, O(6)CH₂Ph], 4.98 [d, J = 12.0 Hz, O(8)CH₂H_bPh], 4.95 [d, J = 12.0 Hz, O(8)CH_aH_bPh], 4.01 [q, J = 7.0 Hz, ArCHCH₃], 3.82 [d, J = 14.0 Hz, NCH₂H_bPh], 3.52 [ddq, J = 10.5, 4.5 and 6.5 Hz, CH₂CH_bCH], 3.32 [d, J = 14.0 Hz, NCH_aH_bPh], 2.63 [dd, J = 17.0 and 10.5 Hz, CH_aCH_bCH], 2.58 [dd, J = 17.0 and 4.5 Hz, CH_aCH_bCH], 1.34 [d, J = 6.5 Hz, CH₃(1)], and 1.26 [d, J = 6.5 Hz, CH₃(3)]; ¹³C NMR (75 MHz, CDCl₃): δ 157.6, 157.1, 137.1, 136.7, 129.0, 128.7, 128.5 [5C], 128.4 [2C], 128.3, 128.0 [2C], 127.9, 127.6 [2C], 126.9 [2C], 126.4, 105.5, 98.3, 70.0, 69.6, 51.2, 50.0, 45.7, 32.6, 19.9, and 19.5; IR (neat NaCl plates): 2967, 1603, 1454, and 1149 cm⁻¹; Anal. calcd for C₃₂H₃₃NO₂: C, 82.90; H, 7.17. Found: C, 82.89; H, 6.95.

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Example 3. Preparation of Iodide (8)

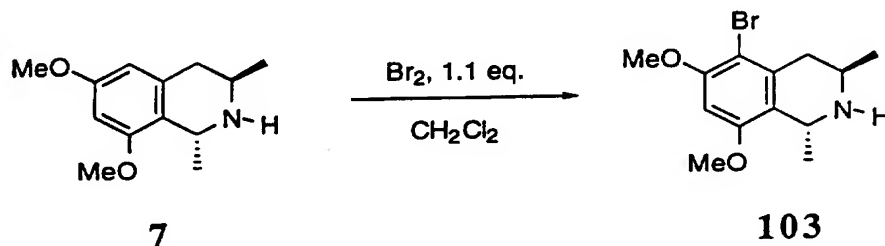


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A solution of compound **102** (0.48 g, 1.0 mmol) in 10 mL of EtOH and 2 mL of CH₂Cl₂ was added slowly to a stirred mixture of iodine (0.53 g, 2.1 mmol) and silver sulfate (0.69 g, 2.2 mmol) in 10 mL of EtOH. After being stirred at room temperature for 16 h, the yellow solid was removed by filtration and the filtrate was concentrated in vacuo. The resulting residue was dissolved in CH₂Cl₂ (100 mL). This solution was washed with saturated NaHCO₃, H₂O, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc; 9:1) to yield iodide **8** (0.40 g, 66 %) as a thick oil; ¹H NMR (500 MHz, CDCl₃): δ 7.49-7.18 [m, benzyl ArH], 6.41 [s, ArH(7)], 5.07 [s, O(6)CH₂Ph], 4.98 [d, J = 12.0 Hz, O(8)CH₂H_bPh], 4.94 [d, J = 12.0 Hz, O(8)CH₂H_aPh], 4.01 [q, J = 6.5 Hz, CHCH₃], 3.82 [d, J = 14.0 Hz, NCH₂H_bPh], 3.51 [ddq, J = 12.0, 4.0 and 6.5 Hz, CH_aH_bCHCH₃], 3.20 [d, J = 14.0 Hz, NCH₂H_aPh], 2.66 [dd, J = 17.5 and 4.0 Hz, CH₂H_bCH], 2.42 [dd, J = 17.5 and 12.0 Hz, CH₂CH_aCH], 1.34 [d, J = 6.5 Hz, CH₃(1)], and 1.31 [d, J = 6.5 Hz, CH₃(3)]; ¹³C NMR (75 MHz, CDCl₃): δ 157.4, 156.1, 141.3, 139.5, 137.1 [2C], 128.9 [7C], 128.5 [2C], 128.2, 127.4 [2C], 127.2 [3C], 126.9, 124.3, 97.7, 71.6, 70.3, 51.9, 50.1, 46.9, 39.3, 20.2, and 20.1; IR (neat NaCl plates): 2971, 1585, 1324, and 1062 cm⁻¹; Anal. calcd for C₃₂H₃₂INO₂: C, 65.20; H, 5.47. Found: C, 65.39; H, 5.73.

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Example 4. Preparation of 5-Bromo-(1*R*, 3*R*)-1,2,3,4-tetrahydro-6,8-dimethoxy-1,3-dimethylisoquinoline (103)



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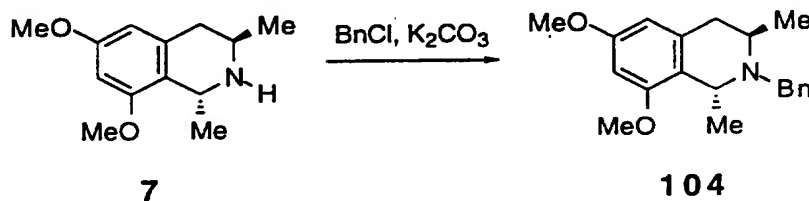
To a solution of tetrahydroisoquinoline **7** (50.0 mg, 0.23 mmol) in CH_2Cl_2 (0.5 ml) was added Br_2 (13 μL , 0.25 mmol). After stirring for 10 min the reaction was diluted with Et_2O , washed successively with with saturated K_2CO_3 , saturated $\text{Na}_2\text{S}_2\text{O}_3$, and brine. The organics were then dried over 4 Å molecular sieves, filtered, and concentrated in vacuo. The resulting residue was triturated with Et_2O and a white solid was filtered (18.4 mg, 27% of brominated tetrahydroisoquinoline **103** as the HBr salt) The remaining material was purified by MPLC (hexanes/ EtOAc ; 1:1 with 3% Et_3N) to yield an additional quantity (39.4 mg, 57%) of the brominated species (84% total); ^1H NMR (200 MHz, CDCl_3): δ 9.6 [vds, 1H, NH], 6.39 [s, Ar-H(7)], 4.84 [q, $J = 6.7$ Hz, CHCH_3], 3.88 [s, OMe], 3.85 [s, OMe], 3.73 [ddq, $J = 11.6, 4.5$, and 6.2 Hz, CH_2CHCH_3], 3.19 [dd, $J = 17.7$ and 4.5 Hz, CHaHbCHCH_3], 2.92 [dd, $J = 17.7$ and 11.6 Hz, CHaHbCHCH_3], 1.81 [d, $J = 6.2$ Hz, CH_2CHCH_3], and 1.70 [d, $J = 6.7$ Hz, CHCH_3]; LRMS (EI): m/z 298 ($\text{M}^+ - 1$, <1), 286 (97), 284 (100), 269, 256, 226, 204, 190, 176, 162, 147, 131, 103, 91, 77, 51, and 42 (all <5).

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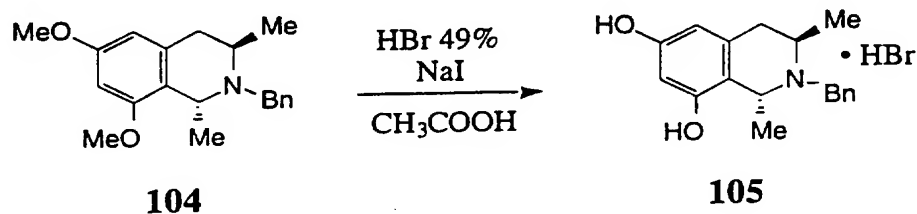
Example 5. Preparation of *N*-benzyl-(1*R*, 3*R*)-1,2,3,4-tetrahydro-6,8-dimethoxy-1,3-dimethylisoquinoline (104)

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Into a stirred solution of (1*R*, 3*R*)-1,2,3,4-tetrahydro-6,8-dimethoxy-1,3-dimethyl-isoquinoline (114 mg, 0.5 mmol) and benzyl chloride (137 mg, 1.1 mmol) in methyl ethyl ketone was added K₂CO₃ (320 mg, 2.3 mmol). The resulting mixture was heated to reflux for 24 h, after which time it was cooled down and poured into H₂O. Et₂O was added and the organic layer was washed with H₂O, brine, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by MPLC (hexanes/EtOAc/Et₃N; 9:1:0.3) to yield N-benzyl-(1*R*, 3*R*)-1,2,3,4-tetrahydro-6,8-dimethoxy-1,3-dimethyl-isoquinoline (148 mg, 93 %) as a colorless oil; ¹H NMR (500 MHz, CDCl₃): δ 7.40-7.20 [m, benzyl ArH], 6.28 [d, J = 2.0 Hz, ArH(7)], 6.23 [d, J = 2.0 Hz, ArH(5)], 3.66 [q, J = 6.5 Hz, ArCHCH₃], 3.82 [d, J = 14.0 Hz, NCH₂H_bPh], 3.78 [s, O(6)CH₃], 3.70 [s, O(8)CH₃], 3.50 [ddq, J = 10.5, 5.0 and 6.5 Hz, CH₂H_bCHCH₃], 3.29 [d, J = 14.0 Hz, NCH₂H_bPh], 2.63 [dd, J = 17.0 and 10.5 Hz, CH₂H_bCH], 2.58 [dd, J = 17.0 and 5.0 Hz, CH₂H_bCH], 1.30 [d, J = 6.5 Hz, CH₃(1)], and 1.25 [d, J = 6.5 Hz, CH₃(3)]; ¹³C NMR (75 MHz, CDCl₃): δ 158.5, 158.4, 141.7, 136.8, 128.4 [2C], 128.1 [3C], 126.4, 104.1, 96.4, 55.2, 55.1, 51.4, 49.8, 45.8, 32.6, 20.0, and 19.5; LRMS (EI): *m/z* 296 (M⁺-CH₃, 100), and 91 (44); IR (neat NaCl plates): 2965, 1605, and 1148 cm⁻¹; Anal. calcd for C₂₀H₂₅NO₂: C, 77.14; H, 8.09. Found: C, 77.30; H, 8.06.

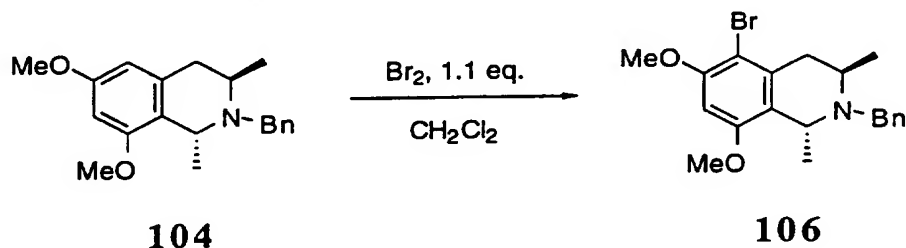
Example 6. Preparation of N-benzyl-(1*R*, 3*R*)-1,2,3,4-tetrahydro-6,8-dihydroxy-1,3-dimethylisoquinoline hydrobromide salt (105)



Into a 15 mL culture tube was placed N-benzyl-(1*R*, 3*R*)-1,2,3,4-tetrahydro-6,8-dimethoxy-1,3-dimethylisoquinoline (62 mg, 0.2 mmol) dissolved in acetic acid (1 mL). To this solution were added sodium iodide (120 mg, 0.8 mmol) and concentrated aqueous hydrobromic acid (49%, 2 mL). The mixture was heated at 100 °C for 3 hours and then cooled to 0 °C, at which time light yellow crystals precipitated out of solution. Vacuum filtration with a glass fritted Buchner funnel gave

the N-benzyl-(1R, 3R)-1,2,3,4-tetrahydro-6,8-dihydroxy-1,3-dimethyl-isoquinoline hydrobromide salt [105] (48 mg, 66%) as light yellow crystals .

5 **Example 7. Preparation of N-benzyl-(1R,3R)-5-bromo-1,2,3,4-tetrahydro-6,8-dimethoxy-1,3-dimethylisoquinoline (106)**

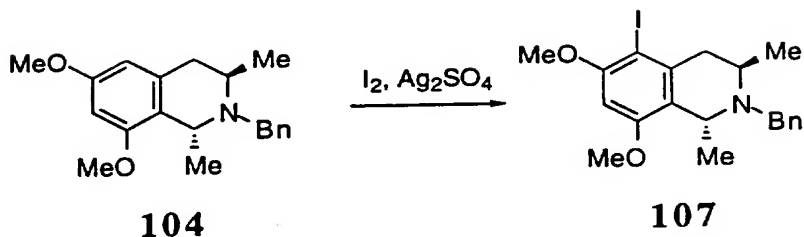


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Into a 25 mL round bottom flask was placed N-benzyl-(1R, 3R)-1,2,3,4-tetrahydro-6,8-dimethoxy-1,3-dimethylisoquinoline (288 mg, 0.9 mmol) dissolved in methylene chloride (3 mL). Bromine (156 mg, 1.0 mmol) in methylene chloride (1 mL) was added to the solution. The mixture was stirred for 3 h at room temperature and then diluted with methylene chloride (20mL) and washed with H₂O (2 x 5 ml). The organic layer was dried with sodium sulfate and concentrated in vacuo to yield 360 mg of crude material. Separation on MPLC (hexane/ethyl acetate; 9:1, 3% Et₃N) gave N-benzyl-(1R, 3R)-5-bromo-1,2,3,4-tetrahydro-6,8-dimethoxy-1,3-dimethylisoquinoline [106] (282 mg, 78%) as light yellow oil; ¹H-NMR (CDCl₃, 200 MHz): δ 7.31 [m, 5H, Ph], 6.4 [s, Ar-H(7)], 3.97 [q, J = 6.6 Hz, CHCH₃], 3.91 [s, OMe] 3.84, [d, J = 14.4 Hz, CH_cH_dPh], 3.76 [s, OMe], 3.52 [ddq, J = 11.6, 6.0, and 4.6 Hz, CH₂CHCH₃], 3.19 [d, J = 14.4 Hz, CH_cH_dPh], 2.74 [dd, J = 17.7 and 4.6 Hz, CH_aH_bCHCH₃], 2.45 [dd, J = 17.7 and 11.6 Hz, CH_aH_bCHCH₃], 1.35 [d, J = 6.0 Hz, CH₂CHCH₃], and 1.31 [d, J = 6.6 Hz, CHCH₃]; ¹³C-NMR (CDCl₃, 200 MHz): δ 157.0, 154.4, 140.9, 136.1, 128.3 [2C], 128.0 [2C], 126.3, 122.1, 104.5, 94.3, 56.3, 55.3 [2C], 51.3, 49.4, 45.7, 33.1, and 19.8; LRMS (EI): m/z 374 (M⁺-15, 70), 360, 294, 268, 226, 203, 190, 162, 145 (all <5), 91 (100), 65, and 39.

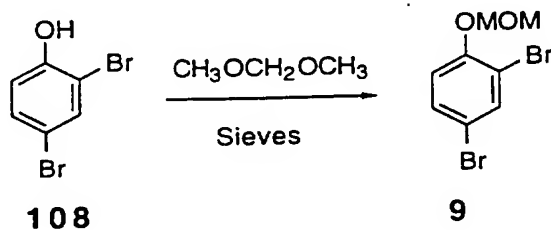
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Example 8. Preparation of Iodide (107)



5 A solution of N-benzyl-(1R, 3R)-1,2,3,4-tetrahydro-6,8-dimethoxy-1,3-dimethyl-isoquinoline (198 mg, 0.61 mmol) in 5 mL of EtOH was added slowly to a stirred mixture of iodine (333 mg, 1.3 mmol) and silver sulfate (468 mg, 1.5 mmol) in 10mL of EtOH. After being stirred at room temperature overnight, the yellow solid was removed by filtration and the filtrate was concentrated in vacuo. The resulting residue was dissolved in 40 mL of CH₂Cl₂. The solution was washed with saturated NaHCO₃, H₂O, dried over Na₂SO₄, and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes/EtOAc; 9:1) to yield iodide **107** (200 mg, 75 %) as a white solid; ¹H NMR (500 MHz, CDCl₃): δ 7.35-7.20 [m, 5H, Ph], 6.36 [s, ArH(7)], 3.90 [q, J = 6.5 Hz, ArCH₂CH₃], 3.89 [s, O(6)CH₃], 3.81 [d, J = 14.5 Hz, NCH₂H_bPh], 3.75 [s, O(8)CH₃], 3.49 [ddq, J = 11.5, 4.5 and 6.5 Hz, CH₂H_bCHCH₃], 3.16 [d, J = 14.5 Hz, NCH₂H_bPh], 2.63 [dd, J = 17.5 and 4.5 Hz, CH₂H_bCH], 2.39 [dd, J = 17.5 and 11.5 Hz, CH₂H_bCH], 1.33 [d, J = 6.5 Hz, CH₃(1)], and 1.29 [d, J = 6.5 Hz, CH₃(3)]; ¹³C NMR (75 MHz, CDCl₃): δ 158.5, 156.8, 141.1, 139.1, 128.4 [2C], 128.1 [3C], 126.4, 123.2, 94.0, 56.6, 55.3, 51.7, 49.6, 46.6, 38.7, 19.9, and 19.8; IR (neat NaCl plates): 2966, 1586, 1453, 1326, 1207, and 1072 cm⁻¹.

Example 9. Preparation of 2,4-Dibromo-1-methoxymethoxybenzene (9)

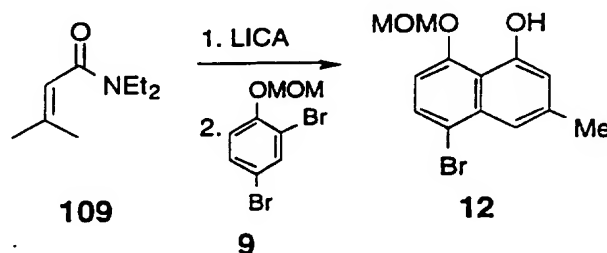


Into a 500-mL round bottom flask equipped with a soxlet and a condensor were placed 2,4-dibromophenol (32.0 g, 0.13 mole), dimethoxymethane (200 mL, 2.26 mole), p-toluenesulfonic acid monohydrate (2.24 g, 12.0 mmol) and CH₂Cl₂ (200 mL). The soxlet extractor was filled with 3 A and 4 A molecular sieves.

- 5 The reaction mixture was heated to reflux for 24 h after which time the soxlet extractor was filled with freshly activated sieves. The reaction mixture was heated to reflux for another 24 h. After this period of time, Et₃N (10 mL) was added. The reaction mixture was stirred for 5 min, and concentrated to dryness. The residue was dissolved in CH₂Cl₂ (400 mL) and the resulting solution was washed with 5 %
10 NaOH (400 mL), H₂O (400 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes/EtOAc; 6:1) to yield 2,4-Dibromo-1-methoxymethoxybenzene [9] (32.9 g, 88 %) as a light yellow oil; ¹H NMR (CDCl₃, 300 MHz) δ 7.67 [s, ArH(3)], 7.33 [d, J = 8.7 Hz, ArH(5)], 7.02 [d, J = 8.7 Hz, ArH(6)], 5.21 [s, OCH₂OCH₃], and 3.49 [s, OCH₃]; LRMS
15 (EI) *m/z* 298 (M⁺, 3), 296 (M⁺, 5), 294 (M⁺, 3), and 45 (100).

Example 10. Preparation of Naphthol (12)

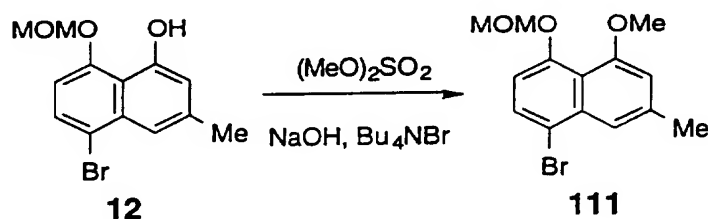
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- To a stirred solution of isopropylcyclohexylamine (7.5 mL, 0.45 mmol) in 60 mL of THF at -78 °C under N₂ was added *n*-BuLi (20.0 mL, 50.0 mmol, 2.5 M in hexanes). The mixture was stirred for 20 min, warmed to 0 °C, and
25 then stirred for 1 h. The mixture was cooled to -78 °C and solution of N,N-diethyl-3,3-dimethylacrylamide (2.10 g, 13.0 mmol) in 40 mL of THF was added. This mixture was stirred at -78 °C for 1 h. The cold bath was removed and the reaction mixture was allowed to warm to -20 °C over a period of 10 min. A solution of 2,4-

dibromo-1-methoxymethoxybenzene (9) in 30 mL of THF was added. The reaction mixture was stirred overnight at room temperature, and then quenched with saturated NH_4Cl . Et_2O was added and the solution was washed with H_2O , brine, dried over Na_2SO_4 , and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes/ EtOAc ; 9:1) to yield naphthol 12 (1.15 g, 29 %) as a brown oil; ^1H NMR (CDCl_3 , 300 MHz): δ 9.31 [s, OH], 7.54 [d, $J = 8.4$ Hz, ArH(6)], 7.49 [s, ArH(4)], 6.82 [s, ArH(2)], 6.81 [d, $J = 8.4$ Hz, ArH(7)], 5.46 [s, OCH_2OCH_3], 3.55 [s, OCH_3], and 2.47 [s, $\text{ArCH}_3(3)$]; ^{13}C NMR (CDCl_3 , 75 MHz): δ 154.3, 153.5, 139.5, 134.5, 129.6, 118.2, 115.5, 114.5, 113.6, 107.3, 95.9, 56.9, and 22.0; LRMS (EI): m/z 298 (M^+ , 13), 296 (M^+ , 11), 128 (5), 115 (9), and 45 (100).

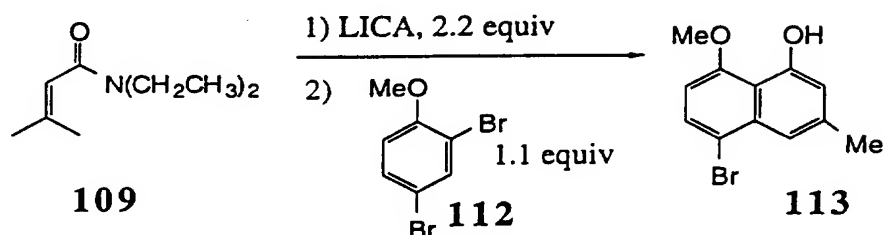
Example 11. Preparation of Bromide (111)



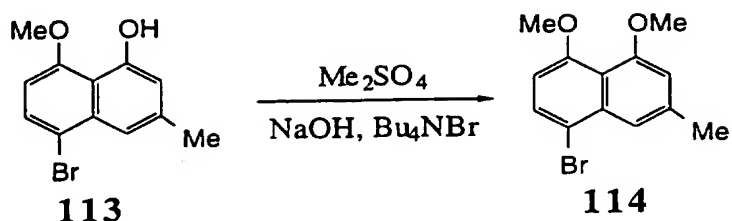
To a stirred solution of dimethyl sulfate (2.49 g, 20.0 mmol) in 20 mL of CH_2Cl_2 was added a solution of Bu_4NBr (2.19 g, 6.8 mmol) and NaOH (0.50 g, 12.0 mmol) in 15 mL of H_2O and a solution of naphthol 12 (1.07 g, 3.6 mmol) in 10 mL of CH_2Cl_2 . The reaction mixture was stirred at room temperature for 18 h. The organic and aqueous layers were separated and the aqueous layer was extracted with 20 mL of CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over Na_2SO_4 , and concentrated in vacuo. The crude product was purified by MPLC (hexanes/ EtOAc ; 9:1) to yield 111 (0.83 g, 74 %) of as a white solid; ^1H NMR (CDCl_3 , 300 MHz): δ 7.63 [s, ArH(5)], 7.62 [d, $J = 8.1$ Hz, ArH(3)], 6.86 [d, $J = 8.1$ Hz, ArH(2)], 6.75 [s, ArH(7)], 5.22 [s, OCH_2OCH_3], 3.94 [s, $\text{ArO}(8)\text{CH}_3$], 3.58 [s, OCH_2OCH_3], and 2.51 [s, $\text{ArCH}_3(6)$]; ^{13}C NMR (CDCl_3 , 75 MHz): δ 156.8, 154.0, 137.8, 135.0, 130.4, 119.5, 118.1, 115.3, 112.9, 109.3, 96.8, 56.5,

56.4, and 22.2; LRMS (EI): m/z 312 (M^+ , 18), 310 (M^+ , 19), 282 (15), 280 (16), 231 (2), 128 (14), and 45(100).

5 **Example 12. Preparation of Compound (113)**



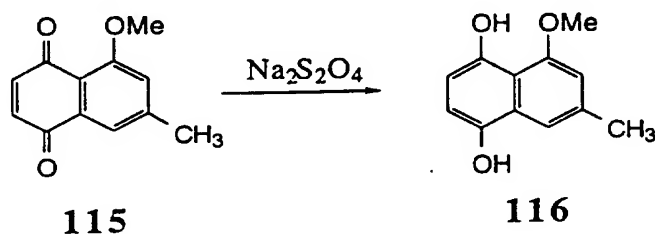
15 In a 250 mL round bottomed flask a solution of
lithiumisopropylcyclohexylamide was prepared from isopropylcyclohexylamine (6.21
g, 7.23 mL, 44 mmol) in THF (50 mL) and butyllithium (2.5 M in hexane, 17.6 mL,
44 mmol). The solution was cooled to - 78 °C under nitrogen and N,N-diethyl-3,3-
20 dimethylacrylamide [109] (3.10 g, 20 mmol) in THF (20 mL) was added. After
stirring for 30 min at - 78 °C, the solution was warmed to room temperature and
stirred for 5 h. The reaction mixture was then cooled to - 78 °C, and 1,4-
dibromoanisole [112] (5.852 g, 22 mmol) in THF (30 mL) was added via syringe.
The solution was stirred at 0 °C for 24 h and then quenched with saturated aqueous
25 ammonium chloride (100 mL) and diluted with ether (30 mL). The organic layer was
separated and the aqueous layer was extracted with ether (3 x 40 mL). The
combined organic layers were washed with brine (40 mL), dried with sodium sulfate
and concentrated in vacuo to give 4.60 g of crude material. Flash chromatography of
the crude material (hexane/ethyl acetate; 9:1) yielded product 113 (1.17 g, 22%) as a
30 light yellow oil .

Example 13. Preparation of Compound (114)

10 A solution of dimethyl sulfate (2.52 g, 20.0 mmol) in methylene chloride (20 mL) was prepared in a 100 mL round bottom flask. To the flask was added a solution of tetrabutyl-ammonium bromide (2.25 g, 7.0 mmol) and sodium hydroxide (400 mg, 10.0 mmol) in water (15 mL). To this mixture was added a solution of compound **113** (1.335 g, 5 mmol) in methylene chloride (10 mL). The reaction mixture was stirred at room temperature for 18 h and then diluted with methylene chloride (20 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with of methylene chloride (20 mL). The combined organic layers were washed with water (10 mL), dried with sodium sulfate, and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexane/ethyl acetate; 9:1) to obtain compound **114** (1.32 g, 94%) as a white solid .

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Example 14. Preparation of Compound (116)

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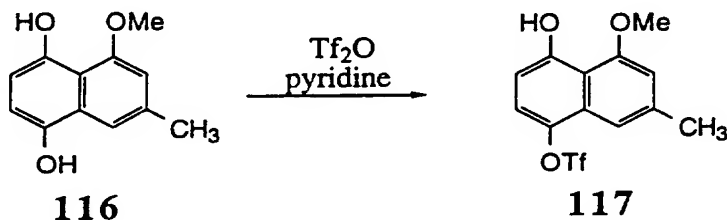
In a 100 mL round bottom flask, 7-methyl-Juglone [**115**] (242.4 mg, 1.2 mmol) was dissolved in chloroform (30 mL). Water (15 mL) and sodium

dithionite (627 mg, 3.6 mmol) were added to this and the mixture was stirred at room temperature for 1 h. When TLC analysis showed no starting material remaining, the organic layer was separated, washed with brine, dried with sodium sulfate and concentrated in vacuo to yield compound 116 (245 mg, 100%) as a white solid.

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Example 15. Preparation of Compound (117)

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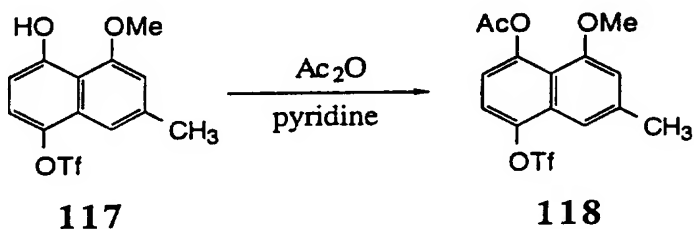


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Compound 116 (204 mg, 1.0 mmol) was placed in a 50 mL round bottom flask with methylene chloride (10 mL) and pyridine (0.32 mL, 4.0 mmol). The mixture was cooled to - 5 °C and triflic anhydride (0.20 mL, 1.15 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. Methylene chloride (20 mL) was added and the mixture was washed with water, dried with sodium sulfate and concentrated in vacuo. Purification by flash chromatography (Hexanes/ethyl acetate; 12:1) yielded product 117 (182 mg, 54%) as a white solid.

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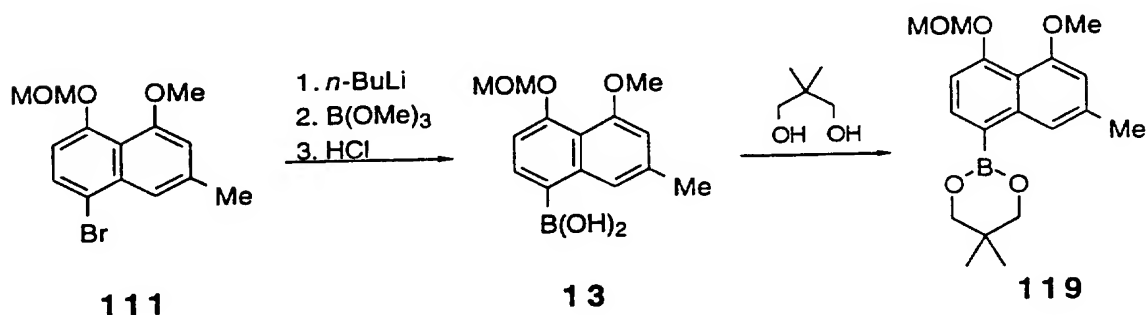
Example 16. Preparation of Compound (118)

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Into a 15 mL round bottom flask was placed monotriflate **117** (50 mg, .
 0.15 mmol) dissolved in methylene chloride (2 mL). To this solution was added
 acetic anhydride (0.04 mL, 0.45 mmol) and pyridine (0.072 mL, 0.90 mmol). The
 reaction mixture was stirred at room temperature for 9 h. When TLC analysis showed
 5 no remaining starting material, the mixture was diluted with methylene chloride (10
 mL), washed with water, dried with sodium sulfate and concentrated in vacuo to give
 compound **118** (56 mg, 100%) as a white solid.

Example 17. Preparation of Boronic Acid (13)

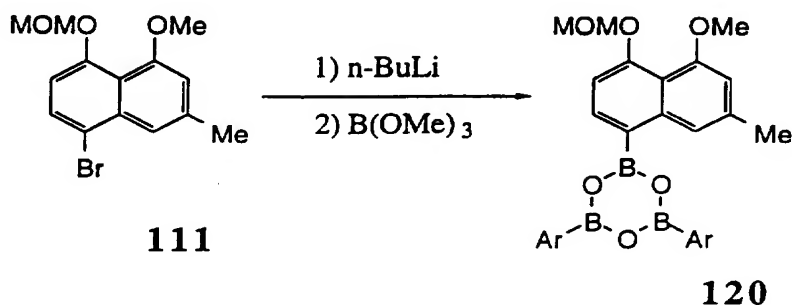
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To a stirred solution of **111** (0.83 g, 2.7 mmol) in 30 mL of THF at
 -78 °C under N₂ was added *n*-BuLi (1.3 mL, 3.2 mmol, 2.5 M in hexanes). The
 resulting mixture was stirred for 15 min and then cannulated into a solution of
 20 B(OMe)₃ (0.65 mL, 5.7 mmol) in 30 mL of THF. The reaction mixture was stirred
 for another 15 min, then warmed to room temperature and stirred for 2 h. The
 reaction mixture was quenched with 10 % HCl, diluted with Et₂O, washed with H₂O,
 brine, dried over MgSO₄, and concentrated in vacuo to yield boronic acid **13** (0.74 g,
 100 %) as a brown solid. This compound was used without further purification. The
 25 structure of boronic acid [**13**] was confirmed by derivatization to boronate ester **119**;
 GC: *t*_R = 13.3 min; column: DB-5, 6 m x 0.1 mm x 0.1 μm film; temp prom: 50 °C /
 2 min / 20 °C min⁻¹ / 250 °C / 10 min; LRMS (EI): *m/z* 344 (M⁺, 100), 314 (46),
 300 (20), 270 (17), and 45 (75).

Example 18. Preparation of Boronic Anhydride (120)



Into a 25 mL flame dried flask was placed bromide **111** (1.10 g, 3.54 mmol) freshly distilled THF (10 mL). Under nitrogen, the solution was cooled to -78 °C and then n-butyllithium (2.5 M in hexane, 1.7 mL, 4.2 mmol) was added. The resulting solution was stirred for 15 minutes, after which time a precipitate appeared. Trimethyl borate (1.7 mL, 14.4 mmol) was added to the flask and a clear solution formed. The mixture was stirred at -78 °C for 30 min and then at room temperature for 2 h. The mixture was quenched with saturated aqueous ammonium chloride (10 mL), concentrated, and diluted with of methylene chloride (20 mL). The organic and aqueous layers were separated and the aqueous layer was neutralized with 10% aqueous hydrochloric acid. The aqueous layer was extracted with methylene chloride (2 x 20 mL), and the combined organics were washed with H₂O (10 mL) and dried over sodium sulfate. Concentration in vacuo yielded 1.0 g of crude material as a caramel colored residue. Precipitation from methylene chloride by addition of hexanes gave the anhydride **120** (548 mg, 60%) as a white solid; ¹H-NMR (CDCl₃, 300 MHz): δ 8.72 [s, ArH(1)], 8.52 [s, J = 7.7 Hz, ArH(7)], 7.08 [d, J = 7.8 Hz, ArH(6)], 6.76 [s, ArH(3)], 5.37 [s, OCH₂OCH₃], 3.97 [s, ArOCH₃], 3.62 [s, OCH₂OCH₃], and 2.43 [s, ArCH₃].

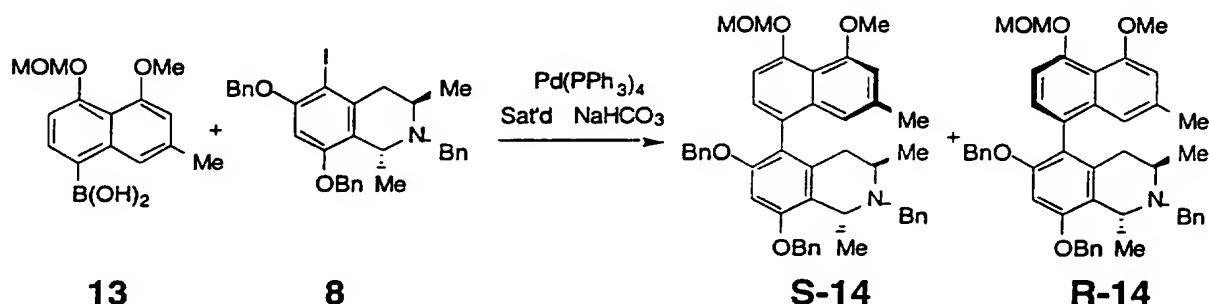
Example 19. General Procedure for the Palladium(0)-Mediated Biaryl Coupling Reactions

To a stirred solution of aryl iodide in toluene (0.05 M) was added 2 equivalents of boronic acid (or its derivatives). Saturated NaHCO₃ (1/2 volume of toluene) was then added, followed by the addition of 20 mol % of Pd(PPh₃)₄. The reaction mixture was sealed under N₂ in a culture tube and heated to 110 °C for 20 h.

- 5 After this period of time, EtOAc and brine were added. The organic layer was extracted, dried over Na₂SO₄, and concentrated in vacuo. The crude product was purified by silica gel chromatography.

A. Preparation of Compound (14)

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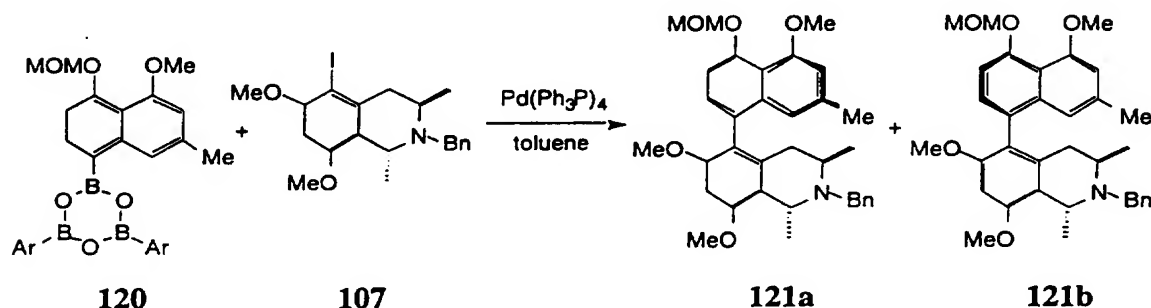


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- Compound **14** was obtained from boronic acid **13** and iodide **8** in 81% yield with a 4:3 ratio of **S-14** to **R-14**. The product was purified by MPLC (hexanes/EtOAc/Et₃N; 3:1:0.1); ¹H NMR of **S-14** (500 MHz, CDCl₃): δ 7.39-6.90 [m, ArH(6' and 7') and benzyl ArH], 6.77 [s, ArH(1')], 6.69 [s, ArH(3')], 6.53 [s, ArH(7)], 5.31 [s, OCH₂OCH₃], 5.02 [s, O(6)CH₂Ph], 4.87 [d, J = 12.5 Hz, O(8)CH₂H_bPh], 4.81 [d, J = 12.5 Hz, O(8)CH_aH_bPh], 4.12 [q, J = 6.5 Hz, PhCHCH₃], 3.98 [s, O(4')CH₃], 3.72 [d, J = 14.5 Hz, NCH₂H_bPh], 3.65 [s, OCH₂OCH₃], 3.37 [ddq, J = 11.5, 4.0, and 6.5 Hz, CH_aH_bCHCH₃], 3.30 [d, J = 14.5 Hz, NCH_aH_bPh], 2.36 [s, CH₃(2')], 2.22 [dd, J = 17.5 and 4.0 Hz, CH₂H_bCH], 2.00 [dd, J = 17.5 and 11.5 Hz, CH_aH_bCH], 1.41 [d, J = 6.5 Hz, CH₃(1)], and 1.01 [d, J = 6.5 Hz, CH₃(3)]; ¹H NMR of **R-14** (500 MHz, CDCl₃): δ 7.39-6.90 [m, ArH(6' and 7') and benzyl ArH], 6.86 [s, ArH(1')], 6.70 [s, ArH(3')], 6.51 [s, ArH(7)], 5.31 [s, OCH₂OCH₃], 5.03 [d, J = 12.0 Hz, O(6)CH₂H_bPh], 4.97 [d, J = 12.0 Hz, O(6)CH_aH_bPh], 4.86 [d, J = 12.5 Hz, O(8)CH₂H_bPh], 4.81 [d, J = 12.5 Hz, O(8)CH_aH_bPh], 4.11 [q, J = 6.5 Hz,
- 20
- 25
- 30

PhCHCH₃], 3.98 [s, O(4')CH₃], 3.77 [d, J = 14.5 Hz, NCH₂H_bPh], 3.65 [s, OCH₂OCH₃], 3.37 [ddq, J = 14.0, 4.0, and 6.5 Hz, CH₂H_bCHCH₃], 3.35 [d, J = 14.0 Hz, NCH₂H_bPh], 2.36 [s, CH₃(2')], 2.25 [dd, J = 17.0 and 14.0 Hz, CH₂H_bCH], 1.92 [dd, J = 17.0 and 4.0 Hz, CH₂H_bCH], 1.39 [d, J = 6.5 Hz, CH₃(1)], and 1.05 [d, J = 6.5 Hz, CH₃(3)]; IR (neat NaCl plates): 2967, 1584, 1052, and 733 cm⁻¹.

B. Preparation of Compound (121)



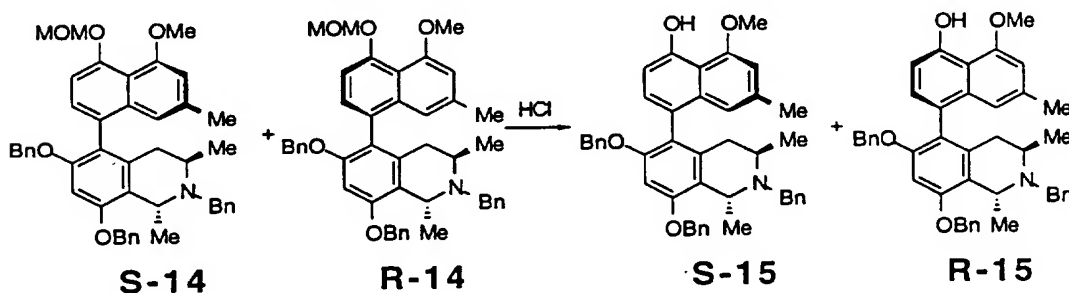
Into a 15 mL culture tube were placed N-benzyl-(1R, 3R)-5-iodo-1,2,3,4-tetrahydro-6,8-dimethoxy-1,3-dimethylisoquinoline [107] (66 mg, 0.15 mmol) and toluene (3 mL). To this solution was added compound 120 (58 mg, 0.23 mmol), which resulted in the formation of a slurry. A minimum amount of ethanol was added to change the slurry to a clear solution. To the resulting solution was added tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.015 mmol) and saturated aqueous sodium bicarbonate (1.5 mL). The atmosphere was exchanged for N₂ and the reaction mixture was heated at 110 °C for 12 hours. When TLC showed no substrate boronate left, the organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine, dried over sodium sulfate and concentrated in vacuo. The resulting residue was purified by silica gel chromatography (hexane/ethyl acetate ; 9:1, 3% Et₃N) to yield a mixture of compounds 121a and 121b (50 mg, 60%) as a white solid; ¹H NMR of 121a (500 MHz, CDCl₃): δ 7.39-7.21 [m, benzyl ArH], 7.17 [d, J = 8.0 Hz, ArH(7')], 7.07 [d, J = 7.5 Hz, ArH(6')], 6.74 [s, ArH(1')], 6.68 [s, ArH(3')], 6.49 [s, ArH(7)], 5.31 [s, OCH₂OCH₃], 4.00 [q, J = 6.5 Hz, NCHCH₃], 3.97 [s, O(4')CH₃], 3.85 [s, O(6)CH₃], 3.72 [d, J = 14.5, NCH₂H_bPh], 3.65 [s, O(8)CH₃], 3.64 [s, OCH₂OCH₃], 3.36 [ddq, J = 11.0, 6.5 and 4.0 Hz, CH₂H_bCHCH₃], 3.26 [d, J = 14.0 Hz, NCH₂H_bPh], 2.35 [s, CH₃(2')], 2.12 [dd, J = 17.5 and 4.0 Hz, CH₂H_bCH], 1.94 [dd, J = 17.5 and 11.0 Hz,

CH₂H_bCH], 1.38 [d, J = 7.0 Hz, CH₃(1)], 1.00 [d, J = 6.5 Hz, CH₃(3)]; ¹H NMR of 121b (500 MHz, CDCl₃): δ 7.39-7.21 [m, benzyl ArH], 7.12 [d, J = 8.0 Hz, ArH(7')], 7.06 [d, J = 8.0 Hz, ArH(6')], 6.79 [s, ArH(1')], 6.69 [s, ArH(3')], 6.48 [s, ArH(7)], 5.30 [s, OCH₂OCH₃], 4.01 [q, J = 6.5 Hz, NCHCH₃], 3.97 [s, O(4')CH₃], 3.84 [s, O(6)CH₃], 3.76 [d, J = 14.0 Hz, NCH₂H_bPh], 3.65 [s, O(8)CH₃], 3.62 [s, OCH₂OCH₃], 3.36 [ddq, J = 12.0, 6.5 and 4.5 Hz, CH₂H_bCHCH₃], 3.31 [d, J = 14.5 Hz, NCH₂H_bPh], 2.35 [s, CH₃(2')], 2.17 [dd, J = 18.0 and 12.0 Hz, CH₂H_bCH], 1.82 [dd, J = 17.5 and 4.5 Hz, CH₂CH_bCH], 1.38 [d, J = 7.0 Hz, CH₃(1)], 1.03 [d, J = 6.5 Hz, CH₃(3)].

Example 20. General Procedure for the Hydrolysis Reactions

To a stirred solution of methoxymethyl-protected starting material in a mixed solvent (MeOH/CH₂Cl₂-10:1, 0.01 M) was added 10 N HCl (1/20 volume of solvent). The reaction mixture was stirred at room temperature for 16 h. After this period of time the solvent was evaporated. EtOAc and saturated NaHCO₃ were added. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The crude product was purified by chromatography.

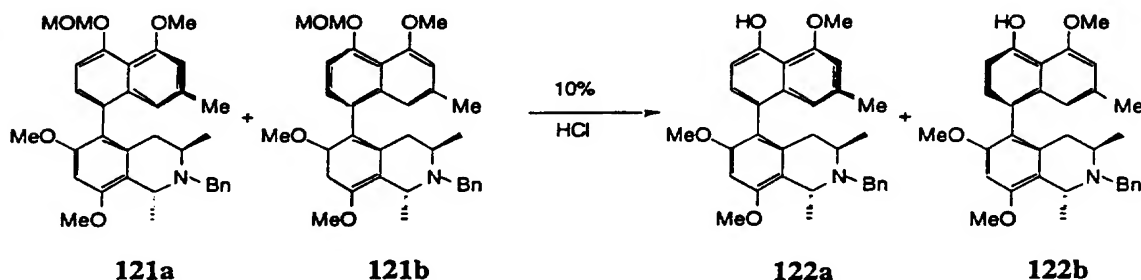
A. Preparation of Compound (15)



Compound 15 was obtained from compound 14 in 71 % yield. The product was purified by MPLC (hexanes/EtOAc/Et₃N; 3:1:0.1); ¹H NMR of S-15 (500 MHz, CDCl₃): δ 9.40 [s, OH], 7.39-6.95 [m, ArH(7') and benzyl ArH], 6.91

[d, $J = 8.0$ Hz, ArH(6')], 6.76 [s, ArH(1')], 6.62 [s, ArH(3')], 6.52 [s, ArH(7)], 5.01 [s, O(6)CH₂Ph], 4.88 [d, $J = 13.0$ Hz, O(8)CH₂H_bPh], 4.82 [d, $J = 13.0$ Hz, O(8)CH₂H_bPh], 4.08 [q, PhCHCH₃, hidden by O(4')CH₃], 4.08 [s, O(4')CH₃], 3.72 [d, $J = 14.0$ Hz, NCH₂H_bPh], 3.37 [ddq, $J = 11.5, 4.0$, and 6.5 Hz, CH_aH_bCHCH₃], 3.29 [d, $J = 14.0$ Hz, NCH₂H_bPh], 2.36 [s, CH₃(2')], 2.21 [dd, $J = 17.5$ and 4.0 Hz, CH₂H_bCH], 1.90 [dd, $J = 17.5$ and 11.5 Hz, CH₂H_bCH], 1.40 [d, $J = 6.5$ Hz, CH₃(1)], and 1.01 [d, $J = 6.5$ Hz, CH₃(3)]; ¹H NMR of R-15 (500 MHz, CDCl₃): δ 9.42 [s, OH], 7.39-6.95 [m, ArH(7') and benzyl ArH], 6.90 [d, $J = 8.0$ Hz, ArH(6')], 6.85 [s, ArH(1')], 6.63 [s, ArH(3')], 6.50 [s, ArH(7)], 5.03 [d, $J = 11.5$ Hz, O(6)CH₂H_bPh], 4.97 [d, $J = 11.5$ Hz, O(6)CH₂H_bPh], 4.87 [d, $J = 13.0$ Hz, O(8)CH₂H_bPh], 4.82 [d, $J = 13.0$ Hz, O(8)CH₂H_bPh], 4.08 [q, PhCHCH₃, hidden by O(4')CH₃], 4.08 [s, O(4')CH₃], 3.77 [d, $J = 14.0$ Hz, NCH₂H_bPh], 3.37 [ddq, $J = 11.5, 4.0$, and 6.5 Hz, CH_aH_bCHCH₃], 3.34 [d, $J = 14.0$ Hz, NCH₂H_bPh], 2.36 [s, CH₃(2')], 2.24 [dd, $J = 17.5$ and 11.5 Hz, CH₂H_bCH], 1.90 [dd, $J = 17.5$ and 4.0 Hz, CH₂H_bCH], 1.38 [d, $J = 6.5$ Hz, CH₃(1)], and 1.05 [d, $J = 6.5$ Hz, CH₃(3)].

B. Preparation of Compound (122)



In a 10 mL round bottom flask, a mixture of substrates **121a** and **121b** (11 mg, 0.02 mmol) was dissolved in methanol (3 mL). To the solution was added 10% aqueous HCl (2 mL) and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated in vacuo and the resulting residue was dissolved in ethyl acetate (10 mL), washed with sodium

bicarbonate, water, and dried over sodium sulfate. Concentration in vacuo yielded a mixture of compounds **122a** and **122b** (10 mg, 100%) as a white solid.

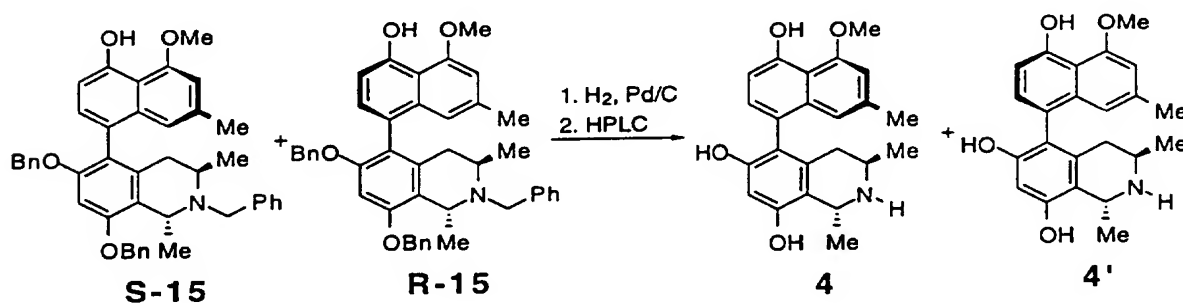
Example 21. General Procedure for the Per-debenzylation Reactions

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To a solution of benzyl-protected monomer in a mixed solvent (MeOH/CH₂Cl₂-2:1, 0.01 M) was added 10 % Pd/C (20 mol %). The atmosphere was exchanged for N₂, then H₂, and then a H₂ balloon was attached. The reaction mixture was stirred until TLC analysis indicated no starting material and possible
 10 intermediate left. The catalyst was removed by passing through a bed of Celite. The filtrate was concentrated in vacuo to yield deprotected monomer. The mixture of atropisomers was able to be separated by HPLC using an amino-bonded column.

A. Preparation of Korupensamine A & "C"

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20

Compound **4** and **4'** were obtained from compounds **15** in 75 % yield. The atropisomers Korupensamine A [**4**] and "Korupensamine C" [**4'**] were separated by HPLC using an amino-bonded column (CHCl₃/MeOH/(NH₄)₂CO₃; 95:5:0.1); ¹H NMR of **4** (HOAc Salt) (500 MHz, CD₃OD, referenced to CHD₂OD @ 3.30 ppm): δ 7.09 [d, J = 8.0 Hz, ArH(7')], 6.80 [d, J = 8.0 Hz, ArH(6')], 6.78 [s, ArH(3')], 6.69 [s, Ar(1')], 6.44 [s, ArH(7)], 4.75 [q, J = 7.0 Hz, ArCHCH₃], 4.08 [s, O(4')CH₃], 3.65 [ddq, J = 12.0, 5.0 and 6.5 Hz, CH₂H_bCHCH₃], 2.62 [dd, J = 18.0 and 5.0 Hz, CH_aH_bCH], 2.30 [s, CH₃(2')], 2.05 [dd, J = 18.0 and 12.0 Hz, CH_aH_bCH], 1.64 [d, J = 7.0 Hz, CH₃(1)], and 1.19 [d, J = 6.5 Hz, CH₃(3)]; ¹H NMR of **4'** (HOAc Salt) (500 MHz, CD₃OD, referenced to CHD₂OD @ 3.30 ppm): δ 7.02 [d, J = 8.0 Hz, ArH(7')], 6.80 [d, J = 8.0 Hz, ArH(6')], 6.80 [s, ArH(1' or 3')], 6.78 [s, Ar(3' or 1')], 6.44 [s, ArH(7)], 4.74 [q, J = 7.0 Hz,

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ArCHCH₃], 4.08 [s, O(4')CH₃], 3.62 [ddq, J = 12.0, 5.0 and 6.5 Hz, CH₂H_bCHCH₃], 2.38 [dd, J = 18.0 and 12.0 Hz, CH₂H_bCH], 2.33 [s, CH₃(2')], 2.23 [dd, J = 18.0 and 5.0 Hz, CH₂H_bCH], 1.67 [d, J = 6.5 Hz, CH₃(1)], and 1.23 [d, J = 6.5 Hz, CH₃(3)].

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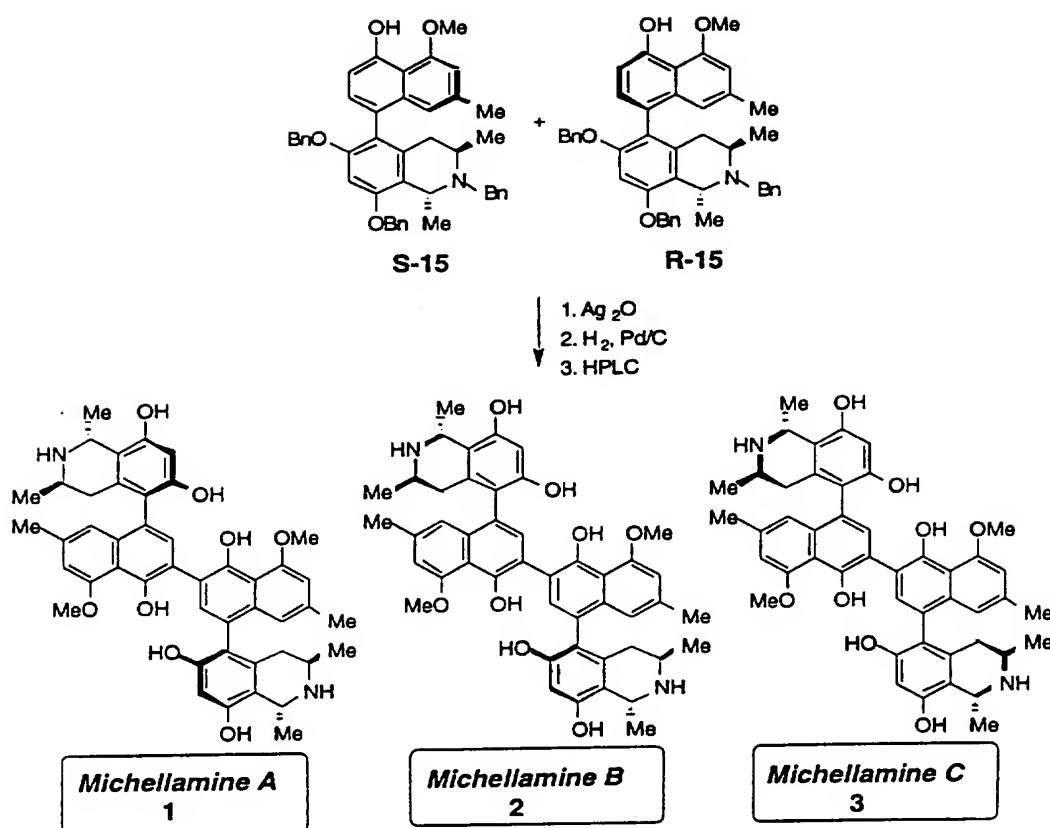
Example 22. General Procedure for the Silver Oxide Promoted Oxidative Coupling and Simultaneous Reductive Bleaching/Perdebenzylation Reactions

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To a stirred solution of benzyl-protected monomer in CH₂Cl₂ (0.01 M) was added 5 equivalent of Ag₂O. The reaction mixture was stirred at room temperature in the dark for 40 h. The solid was removed by passing through the Celite bed. MeOH (volume equal to that of CH₂Cl₂) was added to the filtrate, followed by the addition of 10 % Pd/C (20 mol %). The atmosphere was exchanged for N₂, then H₂, and then a H₂ balloon was attached. The reaction mixture was stirred until TLC analysis indicated no starting material and possible intermediate left. The catalyst was removed by passing through a bed of Celite. The filtrate was concentrated to yield deprotected dimer. The crude product was further purified by HPLC with amino-bonded column.

20

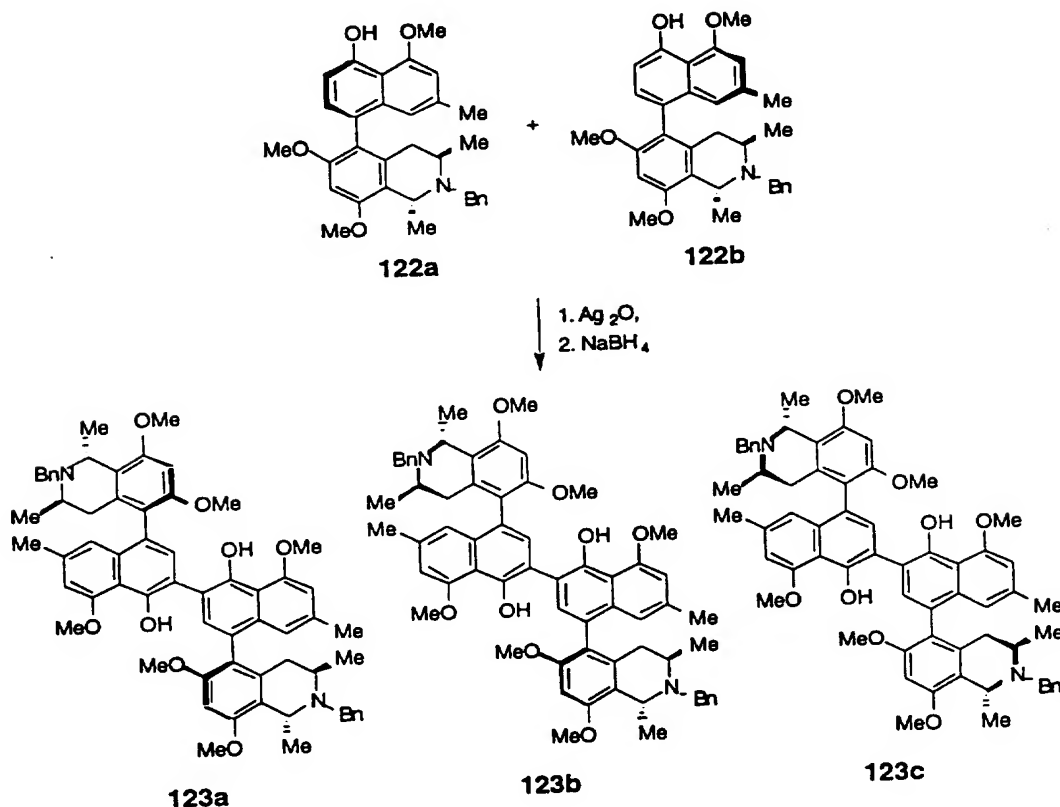
A. Preparation of Michellamines A, B, and C



Michellamines A-C [1-3] were obtained from compound 15 in 90 % yield. They were separated by HPLC using an amino-bonded column

5 (CHCl₃/MeOH/(NH₄)₂CO₃; 93:7:0.1); ¹H NMR of Michellamine A (**1**, HOAc Salt) (500 MHz, CD₃OD, referenced to CHD₂OD @ 3.30 ppm): δ 7.30 [s, ArH(7')], 6.85 [s, ArH(3')], 6.74 [s, ArH(1')], 6.44 [s, ArH(7)], 4.77 [q, J = 7.0 Hz, ArCHCH₃], 4.10 [s, O(4')CH₃], 3.70 [ddq, J = 12.0, 4.5 and 6.5 Hz, CH_aH_bCHCH₃], 2.82 [dd, J = 18.0 and 4.5 Hz, CH_aH_bCH], 2.34 [s, CH₃(2')], 2.15 [dd, J = 18.0 and 12.0 Hz, CH_aH_bCH], 1.65 [d, J = 6.5 Hz, CH₃(1)], and 1.24 [d, J = 6.5 Hz, CH₃(3)]; ¹H NMR of Michellamine B (**2**, HOAc Salt) (500 MHz, CD₃OD, referenced to CHD₂OD @ 3.30 ppm): δ 7.32/7.27 [s, ArH(7')], 6.86/6.74 [s, ArH(3')], 6.85/6.83 [s, ArH(1')], 6.45 [s, ArH(7)], 4.76/4.73 [q, J = 7.0/7.0 Hz, ArCHCH₃], 4.10/4.09 [s, O(4')CH₃], 3.73-3.62 [m, CH_aH_bCHCH₃], 2.79 [dd, J = 17.5 and 5.0 Hz, CH_aH_bCH], 2.53 [dd, J = 18.0 and 11.5 Hz, CH_aH_bCH], 2.36/2.33 [s, CH₃(2')], 2.34-2.29 [dd, CH_aH_bCH, hidden by CH₃(2')], 2.12 [dd, J = 18.0 and 11.5 Hz, CH_aH_bCH], 1.69/1.64 [d, J = 6.5/7.0 Hz, CH₃(1)], and 1.26/1.22 [d, J = 6.0/6.5 Hz, CH₃(3)].

B. Preparation of Compounds (123a), (123b), and (123c)



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In a 10 mL round bottom flask, substrates 122a and 122b (5 mg, 0.01mmol) were dissolved in methylene chloride (3 mL). To the solution was added silver (I) oxide (7 mg, 0.03 mmol) and the mixture was stirred at room temperature overnight. When TLC analysis showed no starting materials were left, the mixture was filtered through a bed of Celite bed. Concentration of the filtrate gave a blue solid (5 mg, 100%) which was dissolved in a mixed solvent of methylene chloride (2 mL) and methanol (2 mL). To the mixture was added a solution of NaBH_4 in methanol (2 mL). The mixture was concentrated, and the residue was dissolved in methylene chloride (10 mL), washed with water, and dried over sodium sulfate.

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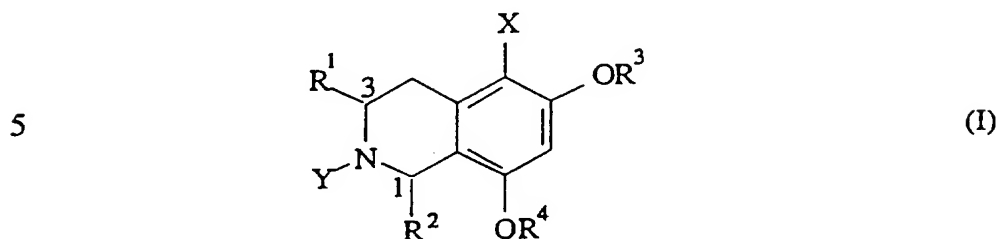
20

Concentration in vacuo yielded a mixture of compounds 123a, 123b, and 123c (5 mg, 100%) as a white solid.

5 It will be appreciated by those skilled in the art that various modifications can be made to the above described embodiments of the invention without departing from the essential nature thereof. The invention is intended to encompass all such modifications within the scope of the appended claims.

33

1. A compound of the formula (I):



10 wherein X is Br, Cl or I, Y is H, (C₁-C₄)alkyl, benzyl, or CHO, each of R¹ and R² is H or CH₃, R³ is H or (C₂-C₅)acyl and R⁴ is a protecting group selected from the group consisting of (C₁-C₄)alkyl, benzyl, (C₂-C₅)acyl and an acid-labile hydroxy protecting group.

- 15 2. The compound of claim 1 wherein R⁴ is an acid-labile hydroxy protecting group.

3. The compound of claim 2 wherein the acid labile protecting group is (C₁-C₄)alkoxy(C₁-C₄)alkyl, tetrahydropyranyl, or (R⁸)₃Si, wherein each R⁸ is (C₁-C₄)alkyl.

- 20 4. The compound of claim 1 wherein R¹ and R² are CH₃.

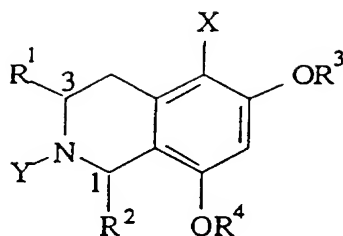
5. The compound of claim 4 wherein C₁ and C₃ have the *R* configuration.

6. The compound of claim 4 wherein X=I.

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7. A compound of the formula (I):

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(I)

wherein X is Br, Cl or I, Y is H, (C₁-C₄)alkyl, benzyl, or CHO, each of R¹ and R² is H or CH₃, R³ is a protecting group selected from the group consisting of (C₁-C₄)alkyl, benzyl, (C₂-C₅)acyl and an acid-labile hydroxy protecting group; and R⁴ is H or (C₂-C₅)acyl.

8. The compound of claim 7 wherein R³ is an acid-labile hydroxy protecting group.

9. The compound of claim 8 wherein the acid labile protecting group is (C₁-C₄)alkoxy(C₁-C₄)alkyl, tetrahydropyranyl, or (R⁸)₃Si, wherein each R⁸ is (C₁-C₄)alkyl.

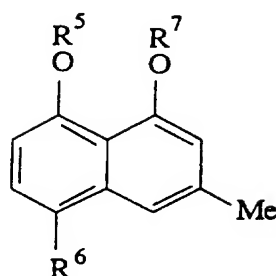
10. The compound of claim 7 wherein R¹ and R² are CH₃.

11. The compound of claim 10 wherein C₁ and C₃ have the *R* configuration.

12. The compound of claim 10 wherein X=I.

13. A compound of the formula (II):

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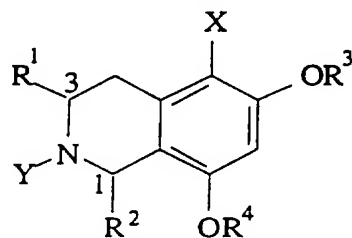


(II)

wherein R^6 is Cl, Br, I, $B(OH)_2$, an anhydride or ester of $B(OH)_2$, or OSO_2R^9 , wherein R^9 is (C_1-C_4) perfluoroalkyl, and each of R^5 and R^7 is H, (C_1-C_4) alkyl, benzyl, (C_2-C_5) acyl or an acid-labile hydroxy protecting group.

14. The compound of claim 13 wherein R^6 is Br or $B(OH)_2$, R^5 is an acid-labile protecting group, and R^7 is H or CH_3 .

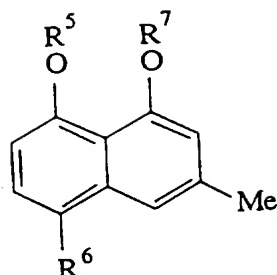
15. A method of preparing a korupensamine or an analog thereof comprising:
(a) reacting a compound of the formula (III):



(III)

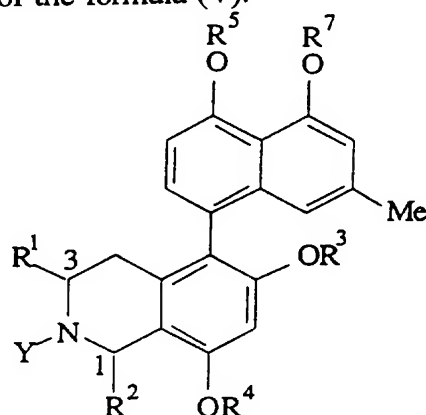
wherein each of R^1 and R^2 is CH_3 or H, X is I, Y is (C_1-C_4) alkyl, benzyl or CHO, and each of R^3 and R^4 is (C_1-C_4) alkyl, benzyl, (C_2-C_5) acyl or an acid-labile hydroxy protecting group; with a compound of the formula (IV):

36



(IV)

wherein R^5 is benzyl, (C_2-C_5) acyl or an acid-labile hydroxy protecting group, R^6 is $B(OH)_2$, and R^7 is (C_1-C_4) alkyl; in the presence of a Pd(0) catalyst and an inorganic base in an organic solvent, to yield a compound of the formula (V):



(V)

wherein Y, R^1 , R^2 , R^3 , R^4 , R^5 and R^7 are as defined above for compounds of formula III and IV.

16. The method of claim 15 further comprising (b) removing protecting groups R^3 , R^4 , R^5 and Y to yield a compound of formula V wherein each of R^1 and R^2 is H or CH_3 , R^7 is (C_1-C_4) alkyl, and Y, R^2 , R^3 , R^4 , and R^5 are H.

17. The method of claim 16 wherein C_1 and C_3 have the *R* configuration.

18. The method of claim 17 wherein the korupensamine prepared is korupensamine A or korupensamine B.
19. The method of claim 15 wherein R^1 , R^2 and R^7 are CH_3 , R^5 is an acid-labile hydroxy protecting group that is subsequently removed by exposing V to dilute aqueous acid, and Y, R^3 and R^4 are benzyl that are subsequently removed by hydrogenolysis.
20. The method of claim 19 wherein R^5 is methoxymethyl.
21. The method of claim 15 wherein C_1 and C_3 have the *R* configuration, R^1 , R^2 and R^7 are CH_3 , Y, R^3 and R^4 are benzyl, and R^5 is an acid-labile hydroxy protecting group, further comprising (b) removing the acid-labile hydroxy protecting group by exposing V to dilute acid and (c) oxidatively coupling two molecules of V to yield *S,S*-16, *R,S*-16 and *R,R*-16 as shown in Fig. 1.
22. The method of claim 21 further comprising (d) reducing the compounds of formula 16 and removing the benzyl groups to yield at least one michellamine.

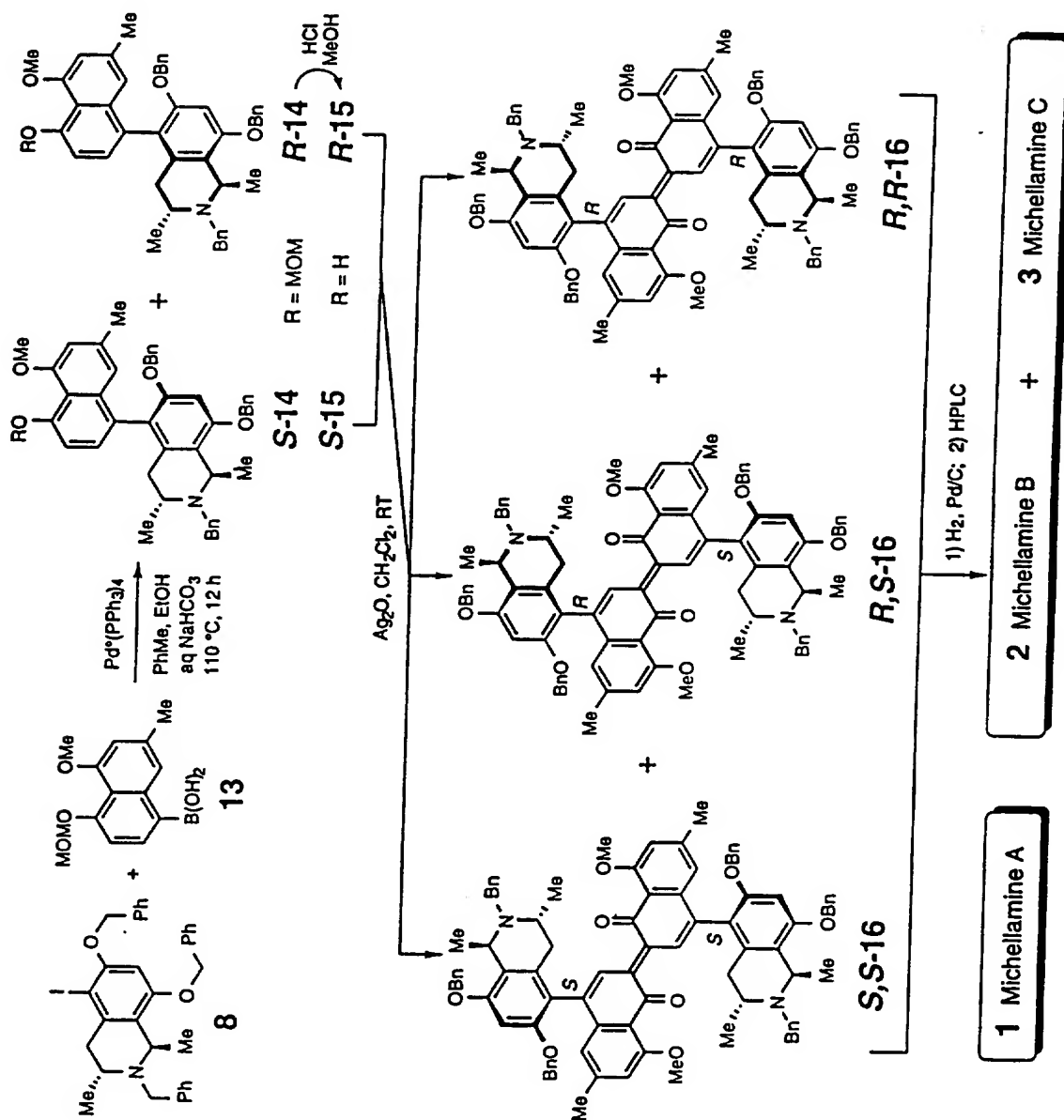


FIG. 1

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/US 95/14896

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D217/24 C07C39/38 C07C309/66 C07F5/02 C07F5/04
C07F5/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF THE CHEMICAL SOCIETY, no. 4, 1963 pages 3940-3945, XP 000561811 HORII Z. ET AL. '748. The synthesis of musizin' see page 3942, formula XVIII ---	13,14
P,X	TETRAHEDRON LETTERS, vol. 35, no. 47, 21 November 1994 pages 8747-8750, XP 000562381 HOYE T.R. ET AL. 'Total synthesis of michellamines A-C: Important anti-HIV agents' see page 8748, compounds 12 and 13	13,14
A	see page 8748, compound 8	1-12
A	see scheme on page 8749 ---	15-22
	-/-	

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

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- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- *&* document member of the same patent family

Date of the actual completion of the international search

11 March 1996

Date of mailing of the international search report

3.04.96

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INTERNATIONAL SEARCH REPORT

Inter. Application No
PCT/US 95/14896

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	HETEROCYCLES, vol. 39, no. 2, 31 December 1994 pages 503-508, XP 000561812 BRINGMANN G. ET AL. 'First total synthesis of korupensamines A and B' see page 505, compound 7	13,14
A	see page 505, compound 10	1-12
A	see scheme on page 506	15-22
A	--- ANGEWANDTE CHEMIE, INTERNATIONAL EDITION IN ENGLISH, vol. 25, no. 10, 1986 pages 913-915, BRINGMANN G. ET AL. 'Regioselective and atropisomeric-selective aryl coupling to give naphthyl iosquinoline alkaloids: The first total synthesis of (-)-ancistrocladine' cited in the application see the whole document	1-12
A	--- AUSTRALIAN JOURNAL OF CHEMISTRY, vol. 43, no. 1, 1990 pages 79-86, XP 000562132 RIZZACASA M.A. ET AL. 'The stereoisomers of 5-bromo-5,8-dimethoxy-1,2,3-trimethyl-1,2, 3,4-tetrahydroisoquinoline: X-ray crystal structure of the trans isomer' see page 80, compounds 18 and 20	1-12
A	--- LIEBIGS ANNALEN DER CHEMIE, 1993 pages 877-888, BRINGMANN G. ET AL. 'The synthesis of all possible isomeric 6,8-dioxygenated 1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin e methyl ethers - useful chiral building blocks for naphthyl iosquinoline alkaloids' cited in the application see the whole document -----	1-12